



KMJ

KUWAIT MEDICAL JOURNAL



The Official Journal of The Kuwait Medical Association

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Editorial

Blood Pressure Normal Levels (Recent AHA Guidelines)

Belle M Hegde

The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*

Manipal University, Manipal, India**

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Anybody who follows the frequent changes in these guidelines in the recent few months is bound to get confused.

The JNCVIII 2013 guidelines come from some of the best brains on the committee, which declared after due consideration, that the normal pressure levels should be at least 159 systolic and 99 diastolic for adults and 140/90 for a diabetic. This looks very reasonable scientifically.

For reasons best known to them, they withheld this revelation for a good four years and released them for public consumption only in 2017; this secret will be revealed later. Immediately after this came a rebuttal from a group of super intelligent American hypertensinologists, that though the guideline committee had given that level, it would be prudent to lower the blood pressure to 130/80 again for all, the reasons are not explained (I shall reveal that later).

Way back in 2005, when JNC V had suggested simple diuretics as the first line of treatment for hypertension, there was a huge hue and cry by a group of self-declared super specialists saying that it is not the ideal drug and that alpha blockers and ACE inhibitors are better drugs; although the JNC V was headed by an eminent specialist who, in his own right, is one of the best in the world. The reason for this above noise is again not explained, and now, any thinking man would get confused. Coming back to the recent guidelines of 130/80 as an ideal blood pressure, one wonders, what on earth is the scientific basis for this recommendation?

In the US, guidelines are mandatory as the so-called modern medicine has got legal monopoly on sickness care. Let us now analyse the rationale for all

these. There are no studies to support these varying claims at different times. Most, if not all, of the above assessment and declarations are subjective personal opinions based on some statistical data which do not apply to individual patients. While the MRFIT study did throw some indirect light on the subject by showing that the lower the blood pressure reading the better the mortality and morbidity rates, but without any cut-off level, according to statistics, zero blood pressure is better than even 10 mm of mercury, but obviously, man will not be alive on 10 mm of mercury. So, this statistic is not reliable. Moreover, there is no evidence in MRFIT data to show that drug induced lowering of blood pressure is good for health. The data shows the normal blood pressure levels in society and not drug induced blood pressure levels. So, this data does not give credence to the claims that we should lower the blood pressure to 130/80 to get better results than keeping it at 140/90. Now it is clear in retrospective that all these guidelines which keep changing frequently are based on individual opinions which have no documented scientific basis.

All these efforts have come about because more and more drug companies have come out with expensive new BP-lowering drugs without any long-term experiential wisdom. Obviously, reasons for various changes in BP guidelines that one gets to know from the above guidelines should have come about because of drug company pressures. It is now known that many guidelines' writers are under the influence of drug companies. They are not God to know what is good and what is not for human beings. I, as a researcher in the area for the last half a century, fail to understand any scientific basis otherwise. May

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**Editor in Chief, ** Cardiologist & Former Vice Chancellor (Retd); #Former Visiting Professor of Cardiology*

##Affiliate Professor of Human Health

God help our hapless patients who swallow these drugs faithfully.

An anecdotal story will illustrate the situation. Two close friends who were classmates from school became doctors. One settled in America as a professor and the other in India as a professor in a medical college. At the age 50, both had what is called elevated BP, which some guidelines warranted drug therapy.

While the Indian friend opted for life style change

and yoga, the American friend opted for drugs as he believed in the American system 100%. He was put on powerful ACE inhibitors and ARBs. Today, after nearly 30 years, the American friend is on daily dialysis as he developed CKD, while his counterpart is still not on anti-hypertensive drugs. Though this anecdote does not support any one view, it gives us a better insight into the mystery of the plethora of data from statistics and how unreliable these linear statistical data are in real life situations.

Original Article

Interscalene Brachial Plexus Analgesia following Arthroscopic Shoulder Surgery: Pharmacodynamics of Bupivacaine Bolus Injection at Different Time Intervals

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Kuwait Medical Journal 2018; 50 (1): 3 - 8

ABSTRACT

Objective: To determine the effect of bupivacaine bolus injection at different time intervals on post-operative pain following arthroscopic shoulder surgery

Design: Double-blinded, randomized, controlled trial

Setting: King Khalid University Hospital, Riyadh, Saudi Arabia

Subjects: Sixty adult patients were classified into three groups with 20 patients each. Ultrasound-guided interscalene block was performed with catheter insertion. In the post-operative period, bupivacaine 0.2% was given as bolus injection at three time intervals every 6, 8 and 12 hours.

Interventions: Numerical rating scale (NRS) was used for pain assessment. Sensory and motor block were assessed before the block, 20 minutes after block, in the post anesthesia care unit (PACU), and at 2, 6, 12, and 24 hours post-

operatively. Patient satisfaction and the analgesic consumption of morphine were assessed in the first 24 hours.

Main outcome measures: There was no statistical difference in the timing of the bolus injection, whether it was given at 6, 8 or 12 hour intervals.

Results: The pain scores were similar in all the groups. In the PACU, the pain scores were 1.4, 1.45 and 1.16. After 24 hours, the pain scores were 1.58, 1.16 and 1.84 in the three groups respectively. Patients and surgeons were satisfied. There was no statistical significance in morphine consumption during the study period among the three groups.

Conclusion: There was no statistical difference in the timing of the bolus injection, whether it was given at 6, 8 or 12 hour intervals; further studies are required with a larger sample size.

KEYWORDS: interscalene block, shoulder surgery, ultrasound

INTRODUCTION

Shoulder surgery results in significant post-operative pain which warrants effective post-operative analgesia. Ultrasound-guided interscalene brachial plexus block (ISBPB) has gained wide acceptance as the preferred method of post-operative analgesia following shoulder surgery^[1]. Local anesthetic administration via a patient-controlled pump was found to decrease the post-operative pain and the need for rescue analgesics^[2]. Commonly, local anesthetics are administered into the interscalene brachial plexus (ISBP) continuously in the post-operative period, followed by removal of the perineural catheter^[3].

Infusion methods exert influence on the course of the operation or the occurrence of adverse effects, as prolonged contact of surrounding tissues with local anesthetic may cause changes in those tissues and may lead to the development of toxicity in the surrounding tissues^[4]. Even with proper procedural technique, ISBPB could lead to post-operative neurological complications in certain cases^[5]. Perineural catheters located precisely at the targeted nerves can supply sufficient analgesia with a small volume of local anesthetics. Current literature suggests a reduction in the volume of local anesthetics used for ultrasound-guided upper extremity blockades^[6]. In one study, it

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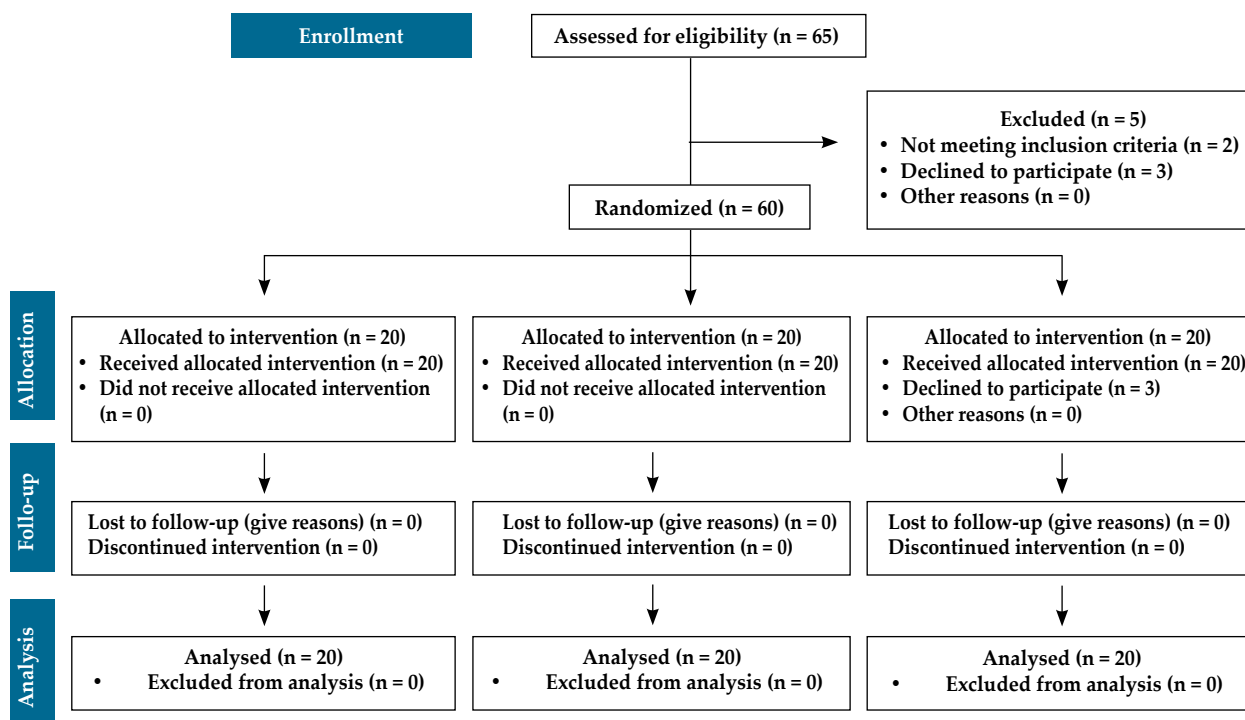


Fig 1: CONSORT chart

was found that single-shot interscalene block with less than 10 ml of ropivacaine in arthroscopic rotator cuff reconstruction reduced post-operative pain for several hours after the operation^[7]. In another study, the authors recommended the use of single-shot interscalene plexus block in combination with patient-controlled catheter system under ultrasound (US) guidance only for the first 24 hours after major open-shoulder surgery^[8]. In the present study, we inserted the perineural catheter into the ISBP with US guidance. Our goal was to investigate the efficacy of the bolus injection method of bupivacaine at different time intervals, and to compare the effects on the quality of analgesia in terms of the total dosage of rescue analgesics given at these time intervals.

SUBJECTS AND METHODS

Patients

After obtaining informed consent from the patients, 60 adult patients (American society of anesthesiologists (ASA) physical status I or II) scheduled for shoulder surgery were included in this double-blinded, randomized, controlled trial. Exclusion criteria included a history of nerve injury, prior trauma to the shoulder, patient on any analgesics for a prolonged period of time to treat other painful conditions and/or allergic to local anesthetic. Patients were randomly classified into three groups with 20 patients each. For randomization, a computerized allocation was

employed. Patients, surgeon and the investigating anesthesiologist were blinded to the allocation of patients to the different groups (Figure 1).

Study protocol

Patients were received at the designated block area within the operating room complex and a complete assessment of the patient was performed. Under routine monitoring like electrocardiography (ECG) and pulse oximetry, an intravenous access was secured and 2 mg of intravenous midazolam was injected. Patient was positioned supine with the face turned to the opposite side of the block. After all aseptic precautions were taken, the neck region was draped with a sterile transparent drape. Sterile ultrasound probe cover and sterile ultrasound gel were employed. A 15-6 MHz 50 mm linear ultrasound probe with the settings to visualize the interscalene muscles and the roots of the brachial plexus in the interscalene groove was used. The anatomy was identified and the view of the roots to be blocked was optimized with settings on the ultrasound machine. A 50 mm 21G needle (Pajunk Medizin technologies, Germany) in which the distal part of the needle, with enhancement of the tip under the ultrasound beam, was introduced in an out of plane approach. When the needle tip was positioned in the desired proximity to the roots, a test dose of 1 ml of normal saline was injected to visualize the spread of the saline and expansion of the interscalene space. 10 ml of

Bupivacaine 0.2% was injected, the catheter provided in the set was introduced through the needle and positioned about 8 to 10 centimeters from the catheter, and was fixed with a transparent dressing. Patients were transferred to the operating room, general anesthetic using a standardized protocol consisting of fentanyl 1 mcg/kg, propofol 2 mg/kg, and tracheal intubation was facilitated with rocuronium 0.6 mg/kg and maintained with 1 MAC sevoflurane. Patients were given further intraoperative analgesia with boluses of fentanyl 50 mcg when the heart rate and blood pressure increased to more than 20 - 25% of the base line measurements. At the termination of surgery, reversal of muscle relaxant after train of four showed adequate recovery (atropine/neostigmine) was given in standard dosages and the trachea was extubated. All patients were transferred to the recovery room for further assessment. Morphine 1 mg/ml through a patient controlled analgesia (PCA) pump with a 10-minute lock-out time and a 1 ml bolus on demand was employed as rescue analgesia. In the post-operative period, patients were injected with boluses of 10 ml of 0.2% bupivacaine in three different time intervals (every 6 hours, every 8 hours and every 12 hours), followed by catheter removal after 24 hours. Afterward and upon discharge, pain was controlled with oral nonsteroidal anti-inflammatory drugs (NSAIDs). None of the patients required opioids before surgery.

Outcome measurements

Data collection included numerical rating scale (NRS) for pain assessment, sensory and motor block assessed at baseline, 20 minutes after block, post-operatively in recovery room, and at 2, 6, 12, and 24 hours post-operatively. Sensation of the upper extremity was assessed by pinprick using a 23-G needle, testing from C5 to T1 dermatomes and scored as full sensation (1) and loss of sensation to touch or pinprick (0). Motor power assessment of the finger flexion (median), finger extension (radial), and finger abduction (ulnar) was scored as movement present (1) and no movement present (0). Patient satisfaction and the analgesic consumption of morphine were assessed in the first 24 hours.

Statistical analysis

We calculated our sample size using Lenth's calculator, version 1.76 (ref), based on the results of a pilot study of 30 patients (10 in each group) that we did using the same protocol. We found the overall mean morphine consumption (+/-SE) was 4.2 +/- 1 mg in the first 24 hours after surgery. Using one-way analysis of variance (ANOVA) test with alpha 0.05, one-sided test, Bonferroni method, and with a power of 80%, the calculated sample size was 20 patients in each group. We assessed the data first for normality of distribution using Shapiro-Wilk test. Normally distributed data were presented as mean \pm standard deviation, and median with 95% confidence interval if not. Kruskal-Wallis test was used to compare the quantitative variables between the different groups if these variables did not follow normal distribution. In case the quantitative variables following normal distribution repeated-measures, ANOVA was employed to compare it within these groups. To assess the difference in time for first reported pain, we used Kaplan-Mayer survival analysis with log rank test. We used Statistical Package for the Social Sciences (SPSS) version 22 software (SPSS Inc., Chicago, IL, USA) for statistical analysis.

Ethics

This prospective, observational study was approved by the local Ethics Committee (King Saud University, Riyadh, Saudi Arabia on 24th March, 2014) Ref.Nr. 13-969.

RESULTS

There was no difference in the demographic characteristics of the study cohort (Table 1). There was no statistically significant ($p = 0.310$) difference in post-operative morphine consumption between the three groups. The mean value of the time to the first PCA morphine was 4 ± 1 hr. The mean (SD) values of post-operative morphine consumption (mg) were 4.2 ± 6.4 , 6.1 ± 7.6 and 6.6 ± 6.6 , in groups A, B, and C, respectively. The mean (SD) values of the pain score were similar in all the groups' baseline (3.35 ± 1 , 4.65 ± 1 and 4.42 ± 1 respectively). At 20 minutes after initiation of the block,

Table 1: Demographic and clinical characteristics

Characteristics	Group A (6 hours)	Group B (8 hours)	Group C (12 hours)	p-value **
Age (years)	41 \pm 15	39 \pm 15	41 \pm 17	0.932
BMI (kg/m ²)	29 \pm 6	27 \pm 4	31 \pm 10	0.204
Male / Female	13/7	17/3	16/4	0.298
ASA score (I/II)	11/9	12/8	15/5	0.393
Duration of surgery (min)*	92 [75, 120]	75 [60, 105]	90 [55, 109]	0.113

*Presented as median with 1st and 3rd interquartile (IQR)

**p-value calculated by Kruskal-Wallis Test

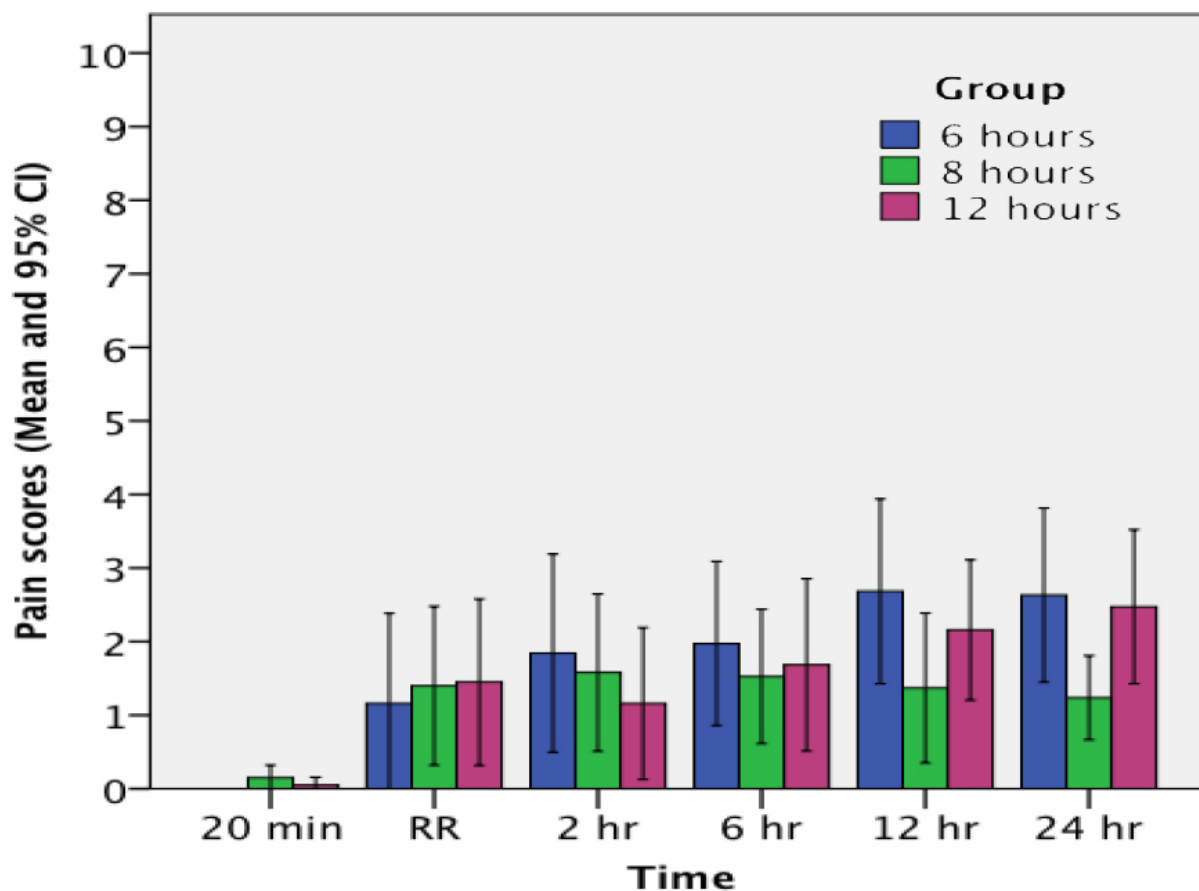


Fig 2: Mean values of postoperative pain scores showed no statistically significant difference between the three groups

it was noted to be 0.15 ± 0 , 0.05 ± 0 and 0, respectively. After patients were transferred to the post anesthesia care unit, the mean \pm SD pain score values were 1.4 ± 0 , 1.45 ± 1 and 1.16 ± 0 in the three groups respectively. After 24 hours, the mean (SD) values of the pain scores were noted to be 1.58 ± 1 , 1.16 ± 0 and 1.84 ± 1 in the three groups respectively. No statistically significant differences in post-operative pain scores ($p = 0.360$) (Figure 2), or the time for first reported pain ($p = 0.293$) were found. There was no statistically significant difference in post-operative heart rate ($p = 0.985$) (Figure 3). Length of hospital stay ($p = 0.515$) and patient satisfaction ($p = 0.346$) showed no statistical differences (Table 2). No side effects like sedation, nausea/vomiting, etc. were reported. Sensory and

motor functions were assessed post-operatively and showed a median of 3 (range: 2 - 5).

DISCUSSION

In this study, we demonstrated a very good perioperative pain relief using US-guided ISBPB following shoulder surgery with bolus injection of 10 ml of bupivacaine 0.2% at different time intervals. This analgesic effect was in accordance with the findings of Fredrickson *et al*^[9,10].

Advanced ultrasound technology is useful for nerve localization and can generate brachial plexus images of high resolution in the interscalene groove, guide block needle placement and advancement in real time to targeted nerves, and assess adequacy of

Table 2: Secondary outcomes comparisons

Outcome measurements	Group A (6 hours)	Group B (8 hours)	Group C (12 hours)	p-value
Length of hospital stay (hours)	28 ± 0.8	27 ± 0.5	28 ± 0.7	0.515
Patient satisfaction				0.346
Not satisfied	1	0	0	
Partially satisfied	0	0	1	
Completely satisfied	11	16	15	

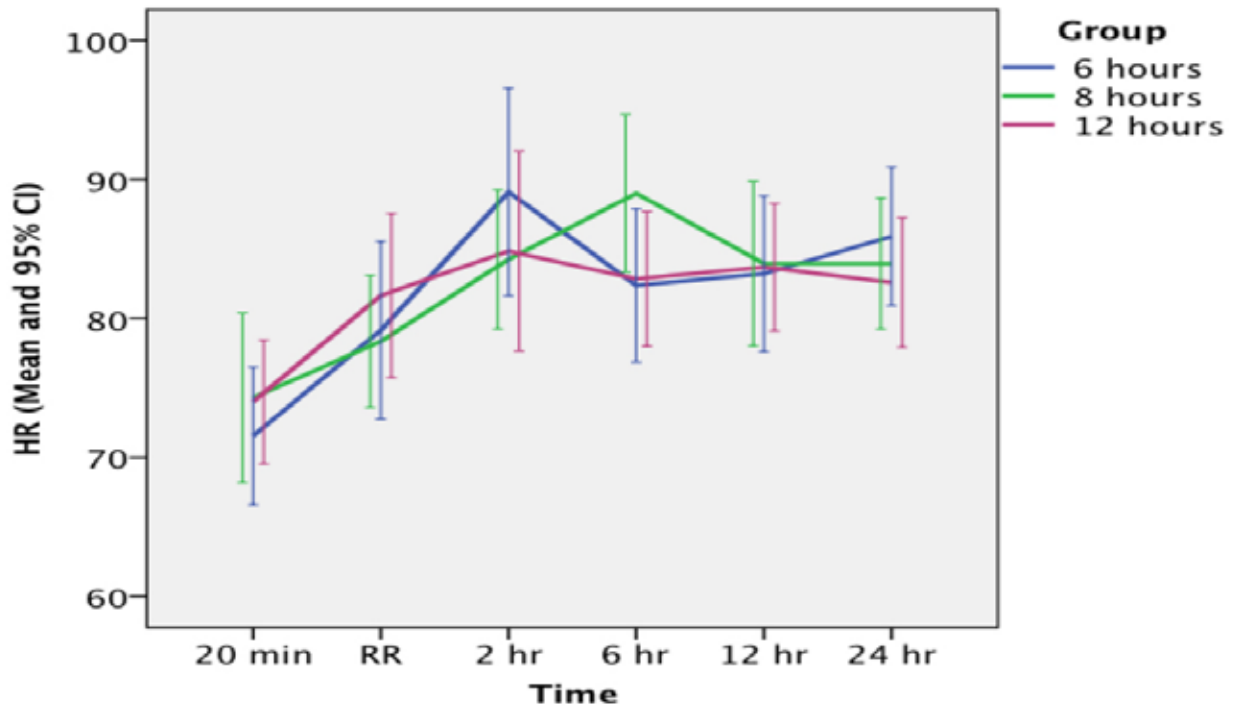


Fig 3: Mean values of postoperative heart rate (HR) in the first 24 hours showed no significant difference between the three groups

local anesthetic spread at the time of injection. Ultrasound imaging guidance can potentially improve success during ISBPB^[11]. Our main finding was that the clinical effectiveness of the plexus block to control post-operative pain required minimal dosage of supplemental morphine. In a similar surgical setting, Borgeat *et al* recently studied interscalene plexus analgesia using a protocol with administration of a local anesthetic as single shot supplemented with patient-controlled additional bolus doses of the same local anesthetic with favorable outcome^[12]. The local anesthetic volume, concentration and timing of injection are important factors to determine the quality of post-operative analgesia and the degree of motor blockade of the limb with subsequent effect on the patient's hospital stay^[13]. In one study on the volume of local anesthetic, it was concluded that the use of low-volume ultrasound-guided ISBPB was associated with fewer respiratory and other complications with no change in the quality of post-operative analgesia compared with the standard-volume technique. They have identified low volume as 5 ml and standard volume as 20 ml of ropivacaine^[14]. Therefore, in the current study, we have defined the low volume as 10 ml of bupivacaine instead. Many published studies compared the effect of different concentrations and volumes of local anesthetic on the quality of post-

operative analgesia. However, few studies described the time interval of the bolus injection technique of the local anesthetic on the quality of post-operative analgesia following shoulder surgery using interscalene approach^[15]. In one study on shoulder arthroscopy, the authors have shown that single-shot interscalene block provides good initial analgesia and that longer term continuous infusions are less likely to be required, as pain can be controlled with simple analgesia in the majority of cases^[16]. Our study showed no statistical difference in the quality of post-operative analgesia and patient satisfaction if the drug is injected either at 6, 8 or 12 hours interval using bolus injection technique. In a systematic review and meta-analysis study, the authors concluded that ISBPB can provide effective analgesia for up to 6 hours with motion and 8 hours at rest after shoulder surgery, with no demonstrable benefits thereafter. In the same study, it was shown that ISBPB can also provide an opioid-sparing effect and reduce opioid-related side effects in the first 12 and 24 hours post-operatively^[17]. Our study has several limitations. First, unfortunately we did not evaluate the analgesic quality during the night, in terms of quality of sleep. Second, a comparison between a bolus injection of the drug by an individual versus patient controlled analgesia method was not studied.

CONCLUSION

The use of low-volume, US-guided ISBPB at different time intervals using the bolus technique is associated with no change in the quality of post-operative analgesia. Further studies are required to prove our results on a larger sample size.

ACKNOWLEDGMENT

Author's contributions: TAZ and MBD designed the study; AEA and AAA performed the study; AA and KAJ analyzed the data; ABN and AE wrote and revised the manuscript. All authors read and approved the final manuscript.

Competing interests: The authors declare no competing interests related to the current study.

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Original Article

Clinical Characteristics of Ruptured Aneurysms in Jilin Province of Northeastern China: An Analysis of 694 Cases

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ABSTRACT

Objective: To investigate the clinical characteristics of ruptured aneurysms in Jilin Province

Design: Retrospective analyses of prospectively recorded data

Setting: Department of Neurosurgery, The First Hospital of Jilin University, Jilin Province, China

Subject: Data collected from 694 cases of ruptured aneurysms in 2014

Intervention: Each patient's basic information, aneurysm characteristics and whether multiple aneurysms had occurred were recorded. A summary of the date and time of the incidence of aneurysmal subarachnoid hemorrhage (aSAH) was noted.

Main outcome measure: This study recorded the characteristics of ruptured aneurysms in Jilin Province and made comparisons with the established tendencies in other studies.

Result: Among the 694 cases, there were high incidence rates of aSAH between March and May and between September

and November, as well as between 5 AM and 8 AM. The condition was more common in females than in males. The diameters of 74.2% of the aneurysms were between 3 and 10 mm. Anterior communicating artery aneurysms (AcoAs) were the most common (accounting for 37.8% of the anterior circulation aneurysms), followed by posterior communicating artery aneurysms (PcoAs), accounting for 27.6% of the anterior circulation aneurysms. Multiple aneurysms accounted for 25.8% of all of the aneurysms. Mirror aneurysms comprised 6% of all of the aneurysms and 23.4% of the multiple aneurysms, which mainly consisted of bilateral PcoAs and bilateral middle cerebral artery aneurysms (MCAs). The above results were consistent with the tendencies of other studies, including the seasonal, daytime, age and gender-female predispositions.

Conclusion: Although this study demonstrates high consistency with other studies, the results are only representative of Jilin Province in China, which indirectly can contribute to the understanding of aneurysm rupture risks.

KEYWORDS: clinical characteristics, Jilin Province, northeastern China, ruptured aneurysm, subarachnoid hemorrhage

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a serious disease, with an overall incidence of approximately 9 per 100,000 person-years worldwide^[1]. The onset of SAH has obvious regional properties^[2]. Japan and Finland have high incidence rates; the incidence rate is 22.7 per 100,000 person-years in Japan and 19.7 per 100,000 person-years in Finland^[1]. Recently, a study in the Korean population showed that the standardized incidence of intracranial aneurysm was 52.2 per 100,000 person-years^[3]. In China, SAH is not uncommon^[4]. In the two communities in Changsha in

the middle of China, the incidence rate was 12.9 per 100 000 person-years^[5]. In addition, the incidence rate in Hong Kong was 7.5 per 100,000 person-years in 2010^[6]. Among these studies, ruptured aneurysms were the main cause of SAH. Currently, there are few epidemiological studies of aneurysmal SAH in China. The status quo of aneurysm treatment in China indicates that aneurysmal SAH is not uncommon in northeastern China^[7].

Jilin Province is located in the central region of northeastern China, between 122 - 131 °E longitude and 41 - 46 °N latitude. The region has a temperate

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monsoon climate, with relatively obvious continental climate features. In the summer, the region has high temperatures and a lot of rain, and in the winter, it is cold and dry^[8]. Ruptured aneurysms in this area may have certain features. The present study retrospectively analyzed SAH cases in Jilin Province caused by ruptured aneurysms that were admitted to the First Hospital of Jilin University in 2014. This analysis can provide information regarding an SAH at this latitude and can provide meaningful epidemiological characteristics for future studies.

SUBJECTS AND METHODS

General information

This study collected the continuous data from aneurysmal subarachnoid hemorrhage (aSAH) cases admitted by the Neurosurgery Department at the First Hospital of Jilin University in 2014 (from January to December), which was a total of 694 cases.

Methods of image examination

When SAH was diagnosed by computerized axial tomography (CT), computed tomography angiography (CTA) was first performed to detect the aneurysms. If the CTA was negative, digital subtraction angiography (DSA) was applied.

Inclusion criteria

The following criteria were used to recruit patients: onset due to simple SAH or combined with intracerebral hematoma; head CTA or DSA confirmed that the SAH was caused by a ruptured aneurysm; and first-time SAH patient.

Exclusion criteria

Patients with the following conditions were excluded from the present study: intracranial arteriovenous malformations combined with aneurysms; Moyamoya disease combined with aneurysms; intracranial arteriovenous fistulas combined with aneurysms; and intracranial pseudoaneurysms after trauma.

Measurement of the aneurysm size

The aneurysm size was calculated using the biggest values of dome length and width.

Data collection methods

The study searched for cases that met the criteria in chronological order in the medical record management system of the First Hospital of Jilin University and recorded each patient's age, gender, previous disease history, onset time, Hunt-Hess grade (a minor revision of the Hunt and Hess scale in 2001)^[9], site of the aneurysm, aneurysm size, whether multiple aneurysms

had occurred and other clinical data.

Statistical methods

SPSS 19.0 statistical software was used for the data processing. The chi-square test was used for the count data analysis, whereas the t-test was used for the measurement data analysis. Differences between the samples were considered statistically significant when p -value < 0.05 .

RESULTS

All patients experienced CTA examinations, 29 (4.2%) patients were negative in the CTA, after which DSA confirmed the presence of an aneurysm in these 29 patients.

Of the 694 patients, 74.2% had single aneurysms (515/694), and 25.8% of the cases had multiple aneurysms (179/694).

Gender characteristics of SAH

There were 694 cases in total, of which 444 cases were female, and 250 cases were male. The ratio between the females and males was 1.8:1. Of the 515 cases of single aneurysms, 313 were in females, and 202 were in males, and the ratio between the females and the males was 1.5:1. Of the 179 cases of multiple aneurysms, 140 were in females, and 39 were in males, and the ratio between the females and males was 3.6:1.

A statistical analysis of the ratios between the males and females showed that there were significant differences ($p < 0.05$).

Age characteristics of SAH

1. Of the 694 cases, the minimum age was 17 years, the maximum age was 87 years, and the average age was 55.3 ± 11.1 years. The average age of the females was 56.7 ± 10.8 years, and the average age of the males was 52.6 ± 11.2 years.
2. Of the 515 cases of single aneurysms, the average age of onset was 54.8 ± 10.9 years. The average age of the females was 56.2 ± 10.7 years, and the average age of the males was 52.6 ± 10.9 years.
3. Of the 179 cases of multiple aneurysms, the average age of onset was 55.5 ± 11 years. The average age of the females was 56.6 ± 10.5 years, and the average age of the males was 51.9 ± 11.9 years. Regardless of the presence of single or multiple aneurysms, the high incidence for both types occurred at approximately 50 - 59 years old. The age of onset was slightly older for women than for men.

The statistical analysis indicated that there were significant differences between the males and females ($p < 0.05$). The detailed information regarding the gender and age of the cases is shown in Figs. 1 - 3.

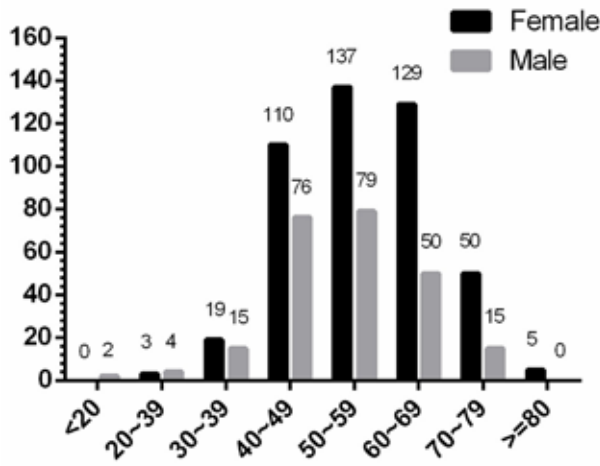


Fig 1: Gender and age distributions of the 694 cases of ruptured aneurysms. In patients older than 30 years, the incidence was more common in women than in men.

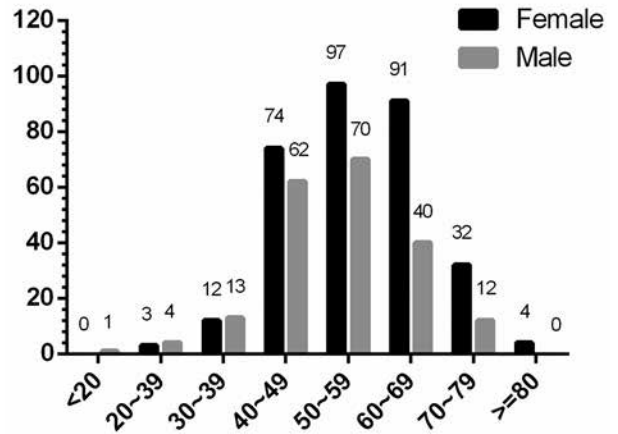


Fig 2: Gender and age distributions of the 515 cases of ruptured single aneurysms. In patients older than 40 years, the incidence was more common in females.

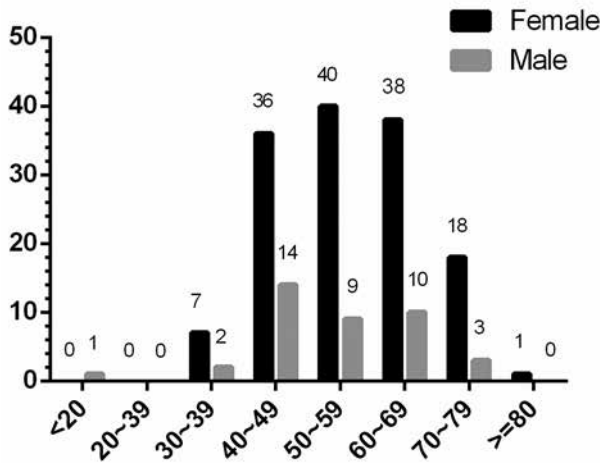


Fig 3: Gender and age distributions of the 179 cases of multiple aneurysms. Women had a higher incidence than men.

Previous disease history

Of the 694 cases, 202 patients had a history of smoking only, 98 patients had a history of hypertension only, and 55 patients had a history of both smoking and hypertension.

1. In the 479 cases with anterior aneurysms, 140 patients had a history of smoking, 68 patients had a history of hypertension, and 38 patients had a history of both smoking and hypertension.
2. In the 36 cases with posterior aneurysms, 10 patients had a history of smoking, 6 patients had a history of hypertension, and 3 patients had a history of both smoking and hypertension.
3. In the 179 cases with multiple aneurysms, 52 patients had a history of smoking, 24 patients had a history of hypertension, and 14 patients had a history of both smoking and hypertension.

There were no statistical differences in the previous disease history between the groups ($p > 0.05$).

Hunt-Hess grading

There were 22 cases of grade I, 126 cases of grade II, 261 cases of grade III, 254 cases of grade IV, and 31 cases of grade V.

Characteristics of the aneurysm size

Regarding the sizes of the ruptured aneurysms, including those of the 515 cases of single aneurysms and the 179 cases of multiple aneurysms (694 cases total), the average size was 5.8 ± 2.7 mm. Of the 694 cases of aneurysms, 15 cases had aneurysms with a diameter ≥ 25 mm, which accounted for 2.2% of the total cases; 70 cases had aneurysms with a diameter between 10 and 25 mm, accounting for 10.1%; 105 cases had aneurysms with a diameter between 7 and 10 mm, accounting for 15.1%; 187 cases had aneurysms with a diameter between 5 and 7 mm, accounting for 27%; 223 cases had aneurysms with a diameter between 3 and 5 mm, accounting for 32.1%; and 94 cases had aneurysms with a diameter < 3 mm, accounting for 13.5%. The sizes of the aneurysms were mainly between 3 and 10 mm (515 cases), accounting for 74.2% of the total cases. For detailed information, see Fig 4.

Characteristics of the aneurysm locations

1. There were 515 cases of single aneurysms, 479 of which were located in the anterior circulation, accounting for 93%, and 36 cases were located in the posterior circulation, accounting for 7%. Among the anterior circulation aneurysms, the most common (181 cases) were anterior

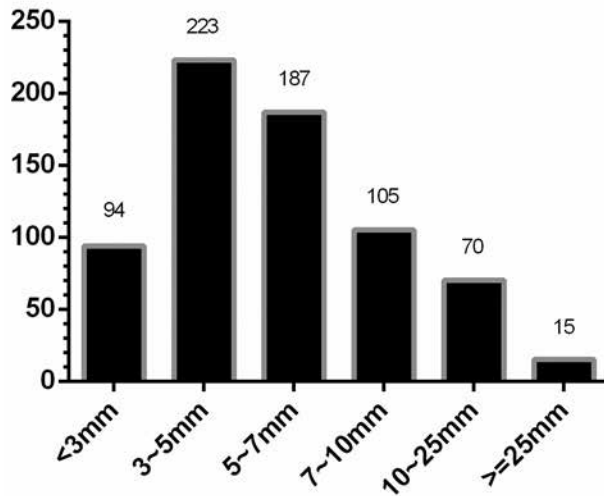


Fig 4: Size distribution of the ruptured aneurysms. Most of the aneurysms were between 3 and 10 mm in size.

communicating artery aneurysms (AcoAs), accounting for 37.8%, followed by 132 cases of posterior communicating artery aneurysms (PcoAs), accounting for 27.6%; 98 cases of middle cerebral artery aneurysms (MCAs), accounting for 20.4%; 42 cases of carotid bifurcation aneurysms, accounting for 8.8%; 25 cases of anterior cerebral artery aneurysms, accounting for 5.2%; and 1 case of distal middle cerebral artery aneurysm, accounting for 0.2%.

Among the posterior circulation aneurysms, basilar artery aneurysms were the most common, accounting for 44.4% (16/36), followed by 14 cases of vertebral artery aneurysms, accounting for 38.9%; 4 cases of posterior cerebral artery aneurysms, accounting for 11.1%; 1 case of posterior inferior cerebellar artery aneurysm, accounting for 2.8%; and 1 case of anterior inferior cerebellar artery aneurysm, accounting for 2.8%.

- There were 179 cases of multiple aneurysms, 42 of which were mirror aneurysms, accounting for 6% (42/694) of all the aneurysms and 23.4% (42/179) of the multiple aneurysms. Additionally, there were 24 cases of bilateral PcoAs, accounting for 13.4% of the multiple aneurysms, and 14 cases of bilateral MCA, accounting for 7.8% of the multiple aneurysms.

Characteristics of the time of onset

- Onset month: There were 30 cases in January, 45 cases in February, 72 cases in March, 80 cases in April, 62 cases in May, 45 cases in June, 50 cases in July, 54 cases in August, 60 cases in September, 76 cases in October, 75 cases in November, and 45 cases in December (Fig 5).

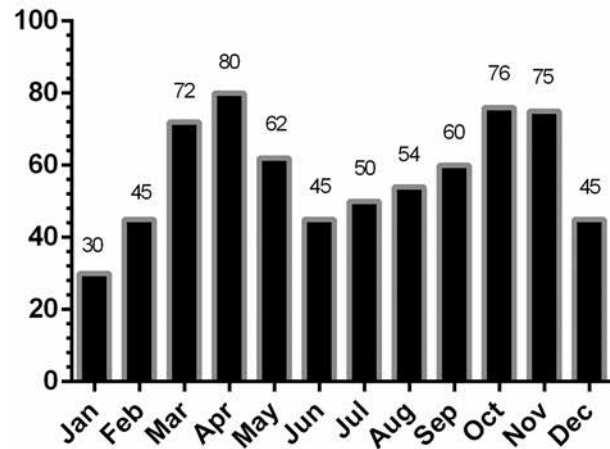


Fig 5: Monthly distribution of the ruptured aneurysms. The condition was more common during the seasonal transitions from winter to spring (March - May) and from autumn to winter (September - November).

cases in October, 75 cases in November, and 45 cases in December (Fig 5).

- Onset timeframe: The onset times for the aneurysms were as follows: 12 AM - 4 AM: 124 cases (17.9%); 5 AM - 8 AM: 152 cases (21.9%); 9 AM - 12 PM: 111 cases (16.0%); 1 PM - 4 PM: 111 cases (16%); 5 PM - 8 PM: 124 cases (17.9%); and 9 PM - 12 AM: 72 cases (10.3%) (Fig 6).

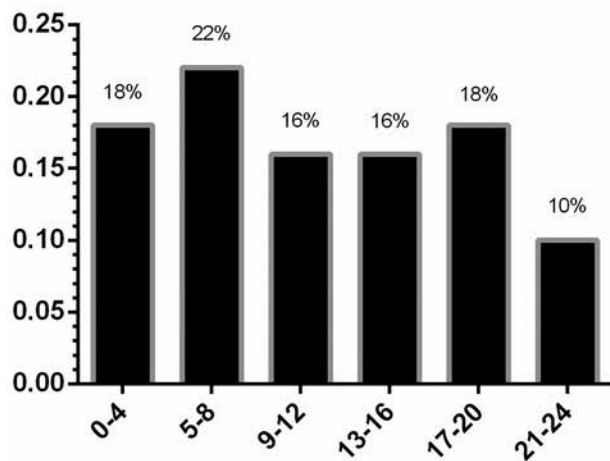


Fig 6: Distribution of the ruptured aneurysms over the different time periods in a single day. The condition was more common between 5 AM and 8 AM.

Onset was common between March and May and between September and November, which are the seasonal transition months, and accounted for 425 cases of the total cases with an incidence of 61.2%. The most common time of onset was between 5 AM and 8 AM, comprising 152 cases, with an incidence of 21.9%.

The statistical analysis showed that there were significant differences ($p < 0.05$).

DISCUSSION

SAH is a bleeding disorder, and 85% of the cases are caused by an aneurysm rupture, which is known as aneurysmal SAH^[10]. The incidence of SAH differs in reports worldwide. Retrospective analyses have suggested that Finland and Japan have the highest incidence rates, whereas South America and Central America have low incidence rates^[11]. There are few epidemiological studies of this condition in China, particularly considering China's large territorial area, which spans an area of approximately 50 degrees in latitude and has a large difference in climate between the south and the north; therefore, a regional study of ruptured aneurysms in China is highly significant. The present study was a retrospective analysis of ruptured aneurysms in Jilin Province in northeastern China. The incidence of SAH may be associated with climate. For example, Finland has a very high latitude and polar day and night is common there; therefore, various climate characteristics may explain the high incidence of SAH. However, climate is only one contributing factor, and according to current evidence, does not influence aneurysm rupture^[12,13]. Many factors can influence aneurysm rupture. For example, estrogen has a protective role against aneurysm rupture in women^[14].

The present study collected 694 continuous cases of ruptured aneurysms from Jilin Province that were treated at the Neurosurgery Department of the First Hospital of Jilin University in 2014. This study is representative of aneurysm ruptures in China because the First Hospital of Jilin University provides the best conditions for cerebral vascular treatment in Jilin Province, and approximately 70% of SAH patients in Jilin Province are treated here each year. The clinical data were analyzed, and the clinical characteristics of aneurysmal SAH of Chinese patients at this latitude and in these climatic zones were summarized. The present study investigated characteristics such as the age, gender, and previous disease history among aneurysm patients in Jilin Province, as well as the aneurysm onset time, Hunt-Hess grade, aneurysm sites, aneurysm sizes and the characteristics of the aneurysms. In this study, after SAH was diagnosed by CT, CTA was first performed to detect the aneurysms because this technique can be performed with high sensitivity (95%) and specificity (97%) for the detection of ruptured aneurysms in the acute setting of SAH^[15]. In the patients who were negative by CTA, DSA further confirmed the presence of the ruptured aneurysms.

Of the 694 patients in the present study, onset was more common between March and May and between September and November. These two time periods represent the seasonal transition periods of autumn to winter and winter to spring in Jilin Province. The incidence of aneurysm rupture was high during the daytime, particularly from 5 AM to 8 AM, which is consistent with a report by Numminen *et al* in Finland in 1996^[16]. Both Jilin Province in northeastern China and Finland have four distinguishable seasons, and the peak onset of SAH occurred during the seasonal transitions; therefore, it is possible that climate change may be a risk factor that affects aneurysm rupture. Of the patients in the present study, the youngest age of onset was 17 years and the oldest was 87 years. The average age was 55 years, whereas the average age of onset for females was 56.7 years, and the average age of onset for males was 52.6 years, which shows that the age of onset was older in females than in males. The older age of onset in females could be because circulating estrogen may inhibit the onset of intracranial aneurysms. The high incidence in women may be because the collagen content in the walls of the cerebral blood vessels decreases significantly after menopause, which promotes the formation of intracranial aneurysms^[17]. The age of onset of aneurysmal SAH can vary in different regions, which may be associated with differences in the average lifespan and the varying risk factors of the populations in different countries. For example, the average age of onset for aneurysmal SAH reported by Lai *et al* in a 2009 study was 59 years^[18], whereas the average age of onset of 945 patients in a 2002 report by Weir *et al* was 46 years^[19].

The present study also analyzed gender differences in aneurysm rupture. The incidence of aneurysm rupture in females was significantly higher than that of males, with a ratio of 1.8:1. In other studies, the incidence among females was also higher than that of males. For example, in a 2001 study in Japan by Osawa *et al*, the ratio of female versus male onset was 1.46:1^[20], and the ratio in the Taiwan area of China was 1.47:1^[21]. Among 1,256 patients in Hebei Province in China in a 2014 report by Lin *et al*, the female-to-male ratio was 1.7:1, which was similar to the ratio of 1.8:1 found in the present study^[22]. The female-to-male ratio for multiple aneurysms was higher than that for single aneurysms (3.6:1) in the present study. Other studies have reported similar findings. For example, in 167 cases in a multiple aneurysm study published in 2015 by Jeon *et al*, the female-to-male ratio was 137:30 (or 4.1:1)^[23]. In another example of a multiple aneurysm study published in 2008 by Baumann *et al*, the female-to-male ratio was 3:1^[24]. Therefore, for aneurysmal

SAH, although the female-to-male ratios are different in different countries and regions, the condition always affects more females than males. Particularly in cases of multiple aneurysms, females account for even higher proportions.

The present study also analyzed the aneurysm sizes. Of the 694 cases, aneurysms with diameters between 3 and 10 mm accounted for 83% of the cases, whereas aneurysms with diameters <3 mm accounted for 9.1%. This finding is consistent with other reports. For example, in a 2014 report from Hebei Province in China published by Lin *et al*, patients with aneurysms of diameters ≤ 10 mm accounted for 90.6%, and patients with aneurysms ≤ 5 mm accounted for 50.9%^[22]. In another example, in a 1983 study published by Kassel *et al*, patients with aneurysms of diameters smaller than 10 mm accounted for 71%, and those smaller than 5 mm accounted for 13%^[25]. Therefore, ruptured aneurysms are mainly smaller in size. In contrast to ruptured aneurysms, a risk analysis of unruptured intracranial aneurysms during a prospective 10-year cohort study found that aneurysms that were ≥ 5 mm were associated with a significantly increased risk of rupture when compared with aneurysms that were 2 - 4 mm in diameter^[26]. For unruptured aneurysms, as the size increases, the rupture risk is higher, particularly for aneurysms measuring 7 mm and above^[27]. However, in this study, the predominant size at the time of rupture was 5 - 7 mm, which suggests that this size may be more common in this population.

The present study also analyzed the locations of the ruptured aneurysms. In the present study, ruptured aneurysms that occurred in the anterior circulation accounted for 93% of the total, of which AcoAs were most common (37.8%), followed by PcoAs (27.6%). Similar conclusions have been reported in Japan and Western countries^[19,20,28]. These findings are also similar to previous studies from Hong Kong and Taiwan^[21,29,30] and to the results reported by Inagawa *et al* in 2006, which found that for ruptured intracranial aneurysms, 90% occurred in the anterior circulation, 40% of which were AcoAs and 25% were PcoAs^[31]. In the present study, there were 179 cases of multiple aneurysms, accounting for 25.8% of the 694 cases of aneurysms. This result was higher than the 17% reported in Hong Kong and the 15% reported in Japan, but was similar to the 30 - 40% reported in Western populations^[32-34].

Among the multiple aneurysms, mirror aneurysms are noteworthy. Most mirror aneurysms are located in the bilateral symmetrical arteries. In a 2006 report, less than 5% of all aneurysms presented as this type of mirror aneurysm^[35]. In a 2012 study, Meissner *et al*

summarized 3120 cases from 61 centers, 376 of which were cases of mirror aneurysms (12%)^[36]. Of the 694 cases in the present study, 42 cases were mirror aneurysms, accounting for 6% of all aneurysms, which is less than the 12% in the above report. Of the multiple aneurysms in the present study, the incidence of mirror aneurysms was 23.4% (42/179). There were 24 cases of bilateral PcoAs, with an incidence of 13.4%, and there were 14 cases of bilateral MCAs, with an incidence of 7.8%. These findings were slightly lower than those reported in relevant studies. For example, in a 2004 study by Casimiro *et al*, there were 83 cases of multiple aneurysms, 30 of which were mirror aneurysms, with an incidence of 40%^[37].

CONCLUSION

The present study suggests that aneurysmal SAH in Jilin Province of the central region of northeastern China has distinct characteristics. Specifically, they frequently occur during the seasonal transition periods from winter to spring and from autumn to winter, as well as in the morning. Aneurysmal SAH also occurs more often in females than in males. The diameters of the ruptured aneurysms are mainly between 3 and 10 mm, and AcoAs are the most common, followed by PcoAs. Among the multiple aneurysms, mirror aneurysms are not uncommon and consist mainly of bilateral posterior communicating aneurysms and bilateral MCAs. This study has some epidemiological significance. The clinical characteristics of the ruptured aneurysms described in the present study are essentially similar to those reported in relevant studies worldwide; however, there are slight differences. Although the study is limited due to the small sample size, the characteristics of aneurysmal SAH in this area can be summarized. This study can provide information on aneurysmal SAH in this area and meaningful epidemiological characteristics for future studies.

Our study confirms similar tendencies from other studies (seasonal, daytime, age and gender-female predispositions); however, although the characteristics of aneurysmal SAH reported in this study are specifically representative of Jilin Province in China, it can indirectly contribute to the understanding of aneurysm rupture risks.

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Original Article

The Effect of Pregnancy on Women's Sexual Function, Body Image and Pelvic Floor Functions

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ABSTRACT

Objective: The aim of this research is to evaluate the effect of pregnancy on women's sexual function, body image and pelvic floor functions.

Design: This is a descriptive and prospective study

Setting: Gynecological diseases and Delivery Clinics of an Education and Research Hospital of Turkey's Ministry of Health.

Subjects: Participants had three appointments: one each in the first trimester, third trimester and in the fourth month of the post-partum period. In the first interview, 169 pregnant women were met and the information relating to their pre-pregnancy period and first trimester were taken. The second interview was conducted with 96 women and was taken during the third trimester. Lastly, 61 women were interviewed in the fourth month of the postpartum period. The data was collected during face-to-face interviews.

Intervention: None

Main outcome measures: The data was collected using the Information Form, The Female Sexual Function Index, Fecal Incontinence Quality of Life Scale, Urogenital Distress Inventory Short Form, Incontinence Impact Questionnaire Short Form and The Body Exposure during Sexual Activities Questionnaire.

Result: The ages of the women in this study ranged from 18 to 39 years, with an average age of 26.21 ± 5.68 years. It was found that 49.2% (n = 30) of the women were nulliparous and 50.8% (n = 31) were multiparous. Problems experienced in sexual intercourse were found to be higher during pregnancy than before pregnancy and the postpartum period. Pregnancy and delivery negatively impact women's sexual function and their body image.

Conclusion: Pregnancy causes urinary incontinence, which can negatively influence women's quality of life.

KEY WORDS: body image, pelvic floor, pregnancy, sexual function

INTRODUCTION

Pregnancy and delivery can be stressful and put a significant burden on women's bodies, even though the female body can physiologically adapt. The physical, social and psychological sexual changes that happen during this process, which starts with the existence of the baby in the mother's womb, and after birth can have a negative impact on couples' lives^[1]. Body image is dynamic and starts to develop in infancy and gains importance during adolescence. It contains the subjective perception of the lifelong development and change of the individual in terms of his/her own body^[2]. Body image changes physiologically in women during different life stages such as adolescence,

pregnancy, postpartum and menopause. Although these processes are normal, problems can arise in how the body is perceived by an individual^[3]. The changes that happen during pregnancy can cause a woman to perceive herself in a different and sometimes negative manner, including being viewed as clumsy, bulky, awkward, ugly, or unattractive. As a result of these changes, a woman's self-confidence and self-respect can decrease and her body image can be negatively affected^[4].

The physical, hormonal, psychosocial and cultural changes that happen during the postpartum period significantly influence the sexual function of women. In the post-delivery period, women can feel tension

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related to their sexuality as they feel physical disorder, fatigue and unwillingness. In the period after delivery, women have more sexual problems compared to pre-pregnancy. It has been determined that women who previously reported sexual problems in the pre-pregnancy period also have sexual problems after delivery^[5]. However, the information on sexuality after delivery that health professionals provide to women is limited to the time of starting a sexual relationship^[6].

Another issue is the effect of the pregnancy and delivery on pelvic floor functions. Delivery is a known risk factor for incontinence in young and middle-aged women, and urinary incontinence is prevalent during pregnancy and after delivery. In the literature, the prevalence of incontinence during pregnancy has been found to be between 23 - 67%^[7]. Research has found that urinary incontinence increases with pregnancy; in addition, the age of the woman during pregnancy and body mass index (BMI) are related to urinary incontinence^[8].

In another study where the relationship of urinary incontinence and pregnancy was investigated, stress incontinence rate in the 3rd trimester was around 40%. In this study, vaginal delivery, prolonged delivery and episiotomy are found to be risk factors for incontinence; no relationship was found between incontinence and women's weight, the age of the pregnant woman or the weight of the fetus. Additionally, this study identified the importance of determining a woman's susceptibility to incontinence before pregnancy to help prevent worsening conditions during pregnancy^[9].

Another problem related to the pelvic floor is fecal incontinence. Fecal incontinence is a disorder that has negative effects on the quality of life. The prevalence of fecal incontinence after pregnancy and delivery is low, and is typically related to risky deliveries^[10]. Furthermore, obstetrical disruption is also listed among the causes of fecal incontinence. One of the most common etiological factors in fecal incontinence is the external and internal anal sphincter disruption that happens during vaginal birth^[11].

The literature mentions pregnancy can increase the risk of fecal and urinary incontinence; in addition, cesarean and vaginal delivery methods pose similar risks for incontinence^[12].

Nurses, physiotherapists, midwives and doctors are the most important members of the multidisciplinary team that contribute to the continuation of a healthy and satisfactory sexuality. This health team can play an important role in the development of the sexual life and body image during a sexual relation by helping women improve their pelvic floor functions during the pregnancy and postpartum periods in their roles as

women's consultants, trainers and maintainers.

SUBJECTS AND METHODS

Design

This descriptive and prospective study was conducted during December 2009 – December 2010 in the Gynecological diseases and Delivery Clinics of an Education and Research Hospital of Turkey's Ministry of Health.

Sample

In determining the sample size for the study, the formula of sample with definite universe was used. A total of 169 women applied to the polyclinics and agreed to participate in the study. Participants had appointments three times, one each in the first and third trimester and in the fourth month of the postpartum period. In the first interview, 169 pregnant women were met and the information relating to their pre-pregnancy period and first trimester was taken. Even though these women accepted to attend a third interview, the researcher could not contact a majority of the women in the first or second interview since they either changed their addresses or the hospitals where they would give birth. The second interview was conducted with 96 women and was taken during the third trimester. Lastly, 61 women were interviewed in the fourth month of the postpartum period.

Ethical considerations

Ethical permission was granted by the ethics board of the hospital (IRB number: 21923). Permission was also granted by the hospital administration, and written informed consent was collected from the participants.

Data Collection

The collected data included sociodemographic variables, general health characteristics, and gynecological-obstetrical story. The Introductory Information Form and Female Sexual Function Index (FSFI) was used for evaluating sexual functions; the Fecal Incontinence Quality of Life Scale (FIQL) was used for determining fecal incontinence, and the Urogenital Distress Inventory Short Form (UDI-6) and Incontinence Impact Questionnaire Short Form (IIQ-7), as well as the Body Exposure during Sexual Activities Questionnaire (BESAQ) were used. For this research, the Turkish language validity and reliability of the BESAQ was used.

In the study, interviews were conducted face-to-face and took approximately 20 - 30 minutes. All of the data in this study was based on the doctoral thesis prepared by primary investigator (HD) under supervision of second investigator (NKB).

Table 1a: Distribution of the data related to the descriptive characteristics of the women who have been met for three interviews (n = 61)

Descriptive characteristics	Min-Max	Mean \pm SS
Age	18 - 39	26.21 \pm 5.68
Marriage Duration (Month/ Year)	0.3 - 18	4.78 \pm 4.5
Education Duration (Year)	0 - 16	7.67 \pm 3.89
BMI before the pregnancy (kg/m ²)	16.97 - 31.63	22.83 \pm 4.18
First Trimester BMI (kg/m ²)	16.89 - 36.6	24.85 \pm 3.94
Gravida (Total Pregnancy Number)	1 - 8	1.85 \pm 1.2
Parity (Number of Pregnancy bigger than 20 hf)	0 - 4	0.57 \pm 0.8
Number of Abortions	0 - 2	0.26 \pm 0.54
D&C (Number of abortion)	0 - 1	0.01 \pm 0.12

Data analysis

Statistical analysis of the data was conducted with the SPSS 20.0 statistics package program. In addition to descriptive statistics (*e.g.*, mean and percentage), a t-test, chi-square test, Friedman Test, Wilcoxon Signed Ranks Test, Repeated Measures ANOVA Test and LSD Test were used. The threshold for statistical significance was $p < 0.05$.

RESULTS

The ages of the women in this study ranged from 18 - 39 years, with an average age of 26.21 ± 5.68 years. All the women in this study were married on average for 4.78 ± 4.5 years. Years of education ranged from 0 - 16 years with an average of 7.67 ± 3.89 years; 47.5% (n = 29) of the women had a primary school education or lower, and 52.4% (n = 32) of the women had a secondary school education or higher (Table 1a, b).

We found 65.6% (n = 40) of the women did not work and 83.6% (n = 51) had social security. Also, the rate of cases whose income was equivalent to their expenses was 62.3% (n = 38) (Table 1a, b).

The average height of the women was 1.61 ± 0.06 meters, and an average pre-pregnancy weight of 59.19 ± 9.48 kg, and an average pre-pregnancy BMI of 22.83 ± 4.18 kg/m². Additionally, the average weight of the 61 women during the first trimester was 64.31 ± 10.62 kg, and their average first trimester BMI was 24.85 ± 3.94 kg/m². We found that 49.2% (n = 30) of women in the first trimester had normal body weights and 39.3% (n = 24) were overweight (Table 1a, b).

In this study, 49.2% (n = 30) of the women were nulliparous and 50.8% (n = 31) of the women were multiparous. We also found that 44.3% (n = 27) of the women had problems during pregnancy, including nausea and vomiting (24.6%, n = 15), inguinal pain (9.8%, n = 6) and low back pain (4.9%, n = 3). Less common problems included epigastric burning, itching and vaginal secretion (Table 1a, b).

When asked about sexual relation problems, 27.8% (n = 47) of the women mentioned having problems

Table 1b: Distribution of the data related to obstetrical characteristics of the women who have been met for three interviews (n = 61)

Obstetrical characteristics	n	%
Marital Status		
Married	61	100
Parity		
Nulliparous	34	55.6
Primiparous	22	36.2
Multiparous	5	8.2
Education		
Primary school and lower	29	47.5
Secondary school and upper	32	52.4
Working Situation		
Non-working	40	65.6
Working	21	34.4
Social Insurance		
Available	51	83.6
Unavailable	10	16.4
Economic Situation		
Income less than expenses	21	34.4
Income equivalent to the expenses	38	62.3
Income more than expenses	2	3.3

before pregnancy. During pregnancy, 54.4% (n = 92) of the women had challenges in the first trimester, 69.8% (n = 67) in the third trimester and 8.2% (n = 5) in the postpartum period (Table 2).

In terms of problems encountered during sexual relations, the women cited pain (57.4%, n = 27) and unwillingness (40.4%, n = 19) before pregnancy. In the first trimester, women cited unwillingness (27.2%, n = 25), fear of causing harm to the baby (27.2%, n = 25), pain during intercourse (9.5%, n = 16) and nausea (6.5%, n = 11). In the third trimester, the major problem was pain during intercourse (38.8%, n = 26), and in the fourth month of the postpartum period, all women experienced pain during intercourse as a significant problem (Table 2).

We found 10.1% (n = 17) of women complained of urinary incontinence before pregnancy. In the first trimester, urinary incontinence was found in 36.1% (n = 61) of the women, and in the third trimester in 46.9% (n = 45); finally, in the postpartum period 11.5% (n = 7) of the women reported a problem with urinary incontinence. Additionally, we found 1.2% (n = 2) of the women had encopresis before pregnancy (Table 2).

We found a statistically significant difference in the BESAQ scale scores between the first trimester, third trimester and fourth month of the postpartum period ($p = 0.002$).

We observed a statistically significant change of 0.23 ± 0.6 unit increase on average in the postpartum fourth month scores when compared to the first trimester scores ($p = 0.004$). We found the rate in which women focused on body image during a sexual relation and avoidance of sexual relations were increased in the fourth month of the postpartum period compared to the first trimester.

Table 2: Distribution of data regarding the sexual function, urinary incontinence and encopresis of the women

Sexual problems	Response	n	%
Having problem during the sexual relation before the pregnancy (n = 169)	Yes	47	27.8
	No	122	72.2
Urinary incontinence before the pregnancy (n = 169)	Yes	17	10.1
	No	152	89.9
Encopresis before the pregnancy (n = 169)	Yes	2	1.2
	No	167	98.8
Having problem during the sexual relation in the 1 st trimester (n = 169)	Yes	92	54.4
	No	77	45.6
Urinary incontinence in the 1 st trimester (n = 169)	Yes	61	36.1
	No	108	63.9
Encopresis in the 1 st trimester (n = 169)	Yes	2	1.2
	No	167	98.8
Having problem during the sexual relation in the 3 rd trimester (n = 96)	Yes	67	69.8
	No	29	30.2
Urinary incontinence in the 3 rd trimester (n = 96)	Yes	45	46.9
	No	51	53.1
Encopresis in the 3 rd trimester (n = 96)	Yes	1	1.1
	No	95	98.9
Having problem in starting the sexual relation in the postpartum period (n = 61)	Yes	5	8.2
	No	56	91.8
Urinary incontinence in the postpartum period (n = 61)	Yes	7	11.5
	No	54	88.5
Encopresis in the postpartum period (n = 61)	Yes	1	1.6
	No	60	98.4

We observed a statistically significant change of 0.26 ± 0.45 unit increase on average in the postpartum fourth month scores when compared to the third trimester scores ($p = 0.001$). The women's rate of conscious focusing during a sexual relation and avoidance in the postpartum fourth month increased compared to the

third trimester. After delivery, the body image of the women was negatively affected (Table 3).

There was a statistically significant change in the FSFI scale scores between the first and third trimesters and the fourth month postpartum scores ($p = 0.016$). In addition, the sexual function of the women was

Table 3: BESAQ scale evaluations (n = 61)

Evaluation period	BESAQ				
	Min	Max	Mean ± SD	X ² / z	p-value
1 st trimester	0.29	2.71	1.29 ± 0.51	12.184 ^a	0.002**
3 rd trimester	0.82	2.18	1.27 ± 0.36		
Postpartum 4 th month	0.79	2.18	1.52 ± 0.47		
Difference 3 rd trimester – 1 st trimester	-1.29	0.93	-0.03 ± 0.51	-0.164 ^b	0.870
Difference postpartum 4 th month – 1 st trimester	-1.32	1.43	0.23 ± 0.6	-2.881 ^b	0.004**
Difference postpartum 4 th month – 3 rd trimester	-0.64	1.29	0.26 ± 0.45	-4.046 ^b	0.001**

^aFriedman test, ^bWilcoxon Signed Ranks Test (Post-Hoc) ** $p < 0.01$

Table 4: FSFI scale evaluations (n = 61)

Evaluation period	BESAQ				
	Min	Max	Mean ± SD	X ² / z	p-value
1 st trimester	2	33.2	20.5 ± 8.33	4.462 ^a	0.016*
3 rd trimester	2	30.2	16.71 ± 9.75		
Postpartum 4 th month	7.4	29.6	20.77 ± 7.21		
Difference 3 rd trimester – 1 st trimester	-26.7	25.9	-3.79 ± 10.6	2.790 ^b	0.021
Difference postpartum 4 th month – 1 st trimester	-20.4	27.5	0.27 ± 10.14	-0.211 ^b	1.000
Difference postpartum 4 th month – 3 rd trimester	-14.9	27.5	4.06 ± 12.18	-2.605 ^b	0.035

^aRepeated Measures ANOVA Test, ^bLSD Test (Post-Hoc), * $p < 0.05$

Table 5: UDI-6 scale evaluations (n = 61)

Evaluation period	BESAQ				
	Min	Max	Mean ± SD	X ² /z	p-value
1 st trimester	0	66.67	18.85 ± 17.01	12.908 ^a	0.001**
3 rd trimester	0	55.56	29.33 ± 13.76		
Postpartum 4 th month	0	50	25.14 ± 13.74		
Difference 3 rd trimester – 1 st trimester	- 61.11	50	10.47 ± 21.3	- 3.700 ^b	0.001**
Difference postpartum 4 th month – 1 st trimester	- 55.56	50	6.28 ± 22.12	- 2.173 ^b	0.030*
Difference postpartum 4 th month – 3 rd trimester	- 55.56	33.33	- 4.19 ± 18.39	- 1.543 ^b	0.123

^aFriedman Test; ^bWilcoxon Signed Ranks Test (Post-Hoc) *p<0.05; **p<0.01

negatively affected in the third trimester (Table 4).

There was a statistically significant change in the direction of 3.79 ± 10.60 unit decrease in the third trimester scores of the women when compared to their first trimester scores (p = 0.021). The rate of sexual function also decreased in the third trimester.

A statistically significant change in the direction of 4.06 ± 12.18 unit increase was observed in the postpartum fourth month scores when compared to the third trimester scores of the women (p = 0.035). Furthermore, the sexual function scores of the women increased and changed in a positive direction.

There was a statistically significant difference in the UDI-6 scale scores in the first and third trimester and the postpartum fourth month scores (p = 0.002). The quality of life of the women in the first trimester was at its highest level when compared to their UDI-6 total scores.

There was a significant change in the direction of 10.47 ± 21.30 unit decrease in the third trimester scores when compared to their first trimester scores (p = 0.001). The women's quality of life was more negatively impacted in the third trimester compared to the first trimester.

We observed a significant change in the direction of 6.28 ± 22.12 unit increase in the postpartum fourth month scores when compared to the first trimester scores (p = 0.030). The women's quality of life was more negatively impacted in the third trimester compared to the fourth month of the postpartum period (Table 5).

We observed a statistically significant change in the first trimester, third trimester and postpartum

fourth month scores of the IIQ-7 scale (p = 0.013). The postpartum fourth month quality of life scores changed positively when compared to the third trimester (Table 6).

There was a significant change in the direction of 3.04 ± 10.51 unit decrease in the postpartum fourth month scores when compared to their third trimester scores (p = 0.006). When compared to the women's IIQ-7 total score averages, their quality of life was negatively affected in the third trimester.

DISCUSSION

Pregnancy is a long process that causes physical (physiological and anatomical), hormonal and psychological changes in a woman's body. The effects of relaxin and progesterone hormones can cause pelvic floor dysfunction. During pregnancy, the hormone progesterone relaxes smooth muscles and reduces their tonus. Relaxin changes and relaxes the connective tissue, thanks to its enzyme effect that melts collagens. In addition, an expanding uterus, maternal weight, altered pelvic connective tissue and changes in the collagen structure can cause pelvic floor dysfunction^[13].

In a study of 518 women from Turkey between the ages of 18 - 55 years by Öksüz and Malhan in 2006^[14], it was reported that 42.9% of the women experienced pain during intercourse. These rates are significantly higher than the dyspareunia in other studies of fertile women based in other countries (8 - 21%)^[15-16]. This study also found dyspareunia occurred at the highest rate (57.4%, n = 27) before pregnancy. According to these results, dyspareunia appears to be a serious

Table 6: IIQ-7 scale evaluations (n = 61)

Evaluation period	BESAQ				
	Min	Max	Mean ± SD	X ² /z	p-value
1 st trimester	0	19.05	1.17 ± 3.55	8.633 ^a	0.013*
3 rd trimester	0	47.62	3.51 ± 10.54		
Postpartum 4 th month	0	4.76	0.47 ± 1.43		
Difference 3 rd trimester – 1 st trimester	-14.29	47.62	2.34 ± 9.78	- 1.821 ^b	0.069
Difference postpartum 4 th month – 1 st trimester	-19.05	4.76	-0.7 ± 3.67	- 1.393 ^b	0.164
Difference postpartum 4 th month – 3 rd trimester	- 47.62	4.76	-3.04 ± 10.51	- 2.754 ^b	0.006**

^aFriedman Test; ^bWilcoxon Signed Ranks Test (Post-Hoc); *p < 0.05; **p < 0.01

health problem for women in our country.

Body image and sexual function are integral parts of good quality of life for women and men. Anxiety during intercourse, focusing on one's appearance and avoidance of certain positions are behaviors that can damage sexual function^[17]. In parallel to the established literature, this study determined a weak, negative relationship between body image during intercourse, and sexual function; when the woman focused less on body image and avoidance of intercourse decreased, sexual function improved.

In the 99-case prospective study that Eason *et al* conducted in 2004^[18], urinary incontinence rates were found to be 22.3% before pregnancy, 65.1% during pregnancy and 31.1% after pregnancy. In the literature, the incontinence prevalence in pregnancy was found to be between 26–58%. In studies of the first year after delivery, urinary incontinence was found to be at a rate of 13–38%^[19]. In our study, the urinary incontinence rate was 10.1% in the pre-pregnancy period, 36.1% in the first trimester, 46.9% in the third trimester, and 11.5% in the postpartum fourth month; these findings are in agreement with established literature.

In a realized study by Demirci *et al* in 2012^[20], urinary incontinence and quality of life was evaluated in women over the age of 18 years. This study found urinary incontinence occurs in one of every four women (26.6%) and quality of life was negatively impacted in these women. Women with urinary incontinence have a lower quality of life compared to women without incontinence. Additionally, in this study, the UDI-6 total average score of the women in their third trimester was at its highest level and negatively impacted quality of life; in addition, the UDI-6 total score average decreased in the postpartum fourth month and quality of life increased (Tables 4 and 5). Similarly, when compared to the women's IIQ-7 averaged total scores, quality of life was in a negative direction in the third trimester ($p = 0.006$; Tables 4 - 6). These findings parallel previously published literature.

It was determined that problems during intercourse occurred more in the pregnancy period compared to the pre-pregnancy and postpartum period ($\chi^2 = 53.79$, $p = 0.001$). According to the women's UDI-6 total scores, their quality of life was at the highest in the first trimester ($\chi^2 = 12.908$, $p = 0.001$); according to the women's IIQ-7 total score averages, quality of life was negatively impacted in the third trimester ($\chi^2 = 8.633$, $p = 0.013$). This study also found that the women's quality of life partly depended on the instance of urinary incontinence in the fourth month of the postpartum period, as well as the third trimester, where there was a negative impact on quality of life.

Fecal incontinence has been observed in 1.5 - 2%

of the adult population. If it includes staining, the instance of fecal incontinence increases to 5%. While vaginal post-delivery anal incontinence is observed between 0.04 - 5% of the cases, this rate increases to 17 - 57% in anal sphincter disruption (even though it is repaired)^[21]. Additionally, in the study, the fecal incontinence rate among the 61 cases was determined as 1.6% ($n = 1$), which is similar to previous literature.

CONCLUSION

The study results showed that frequent urinary incontinence was most seen in the third trimester of pregnancy. The biggest negative effect on women's sexual function was seen in the third trimester of pregnancy. In addition, focusing on body image during sexual intercourse and avoiding intercourse for this reason were most frequent in the fourth postpartum month, compared to the first and third trimester.

As a result, pregnancy and delivery negatively impact women's sexual function and their body image. Pregnancy causes urinary incontinence, which can negatively influence women's quality of life. It is proposed that during the antenatal evaluation, anamnesis should be taken in terms of the sexual relation frequency of the pregnant women, problems during intercourse, urinary incontinence and encopresis. The health team members giving antenatal maintenance service should approach pregnant women in an integrated manner.

Study Limitations

Several factors during this study had the potential to negatively influence the study results. Limitations included that the study was conducted at a single medical center and with a relatively small sample, and the data depended on only self-report measures and retrospective memory.

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Original Article

Smoking Behavior among Male Students in Secondary Schools in Khartoum Locality- Sudan

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ABSTRACT

Objective: To investigate smoking related behaviour and to assess the smoking prevalence among male students in secondary schools in Khartoum locality, Sudan

Design: Cross-sectional study

Setting: The study was carried out at secondary schools in Khartoum, Sudan

Subjects: The study included male students randomly selected from 12 secondary schools from four administrative units of Khartoum.

Intervention: The data were collected using a pre-tested, structured questionnaire to collect information.

Main outcome measures: Determining overall smoking prevalence and the factors which were associated with smoking among students

Results: The study showed that the overall smoking prevalence was 12.9% among the students, majority of them (75.5%) were mainly cigarette smokers. Of students

who smoke, 54.5% started smoking during primary school. The highest percentage (42.9%) claimed smoking was due to smoker friends, while about a third of smoker students reported that they started smoking because they have a smoker in their family. However, a majority of them smoke in public places (63.3%). Forty eight (98%) of the smoking students wanted to quit smoking. The reason they were ready to quit smoking was to save their health (64.6%). This study demonstrated that socio-demographic characteristics like age, class level, family size, monthly income and having a smoker among family members was significantly associated with smoking among school students ($p < 0.5$), whereas, no significant associations were observed between fathers and mothers educational level.

Conclusion: To reduce the prevalence of smoking, intensive interventional measures should target parents, teachers and students and should start as early as in primary schools.

KEYWORDS: cigarette smoking, secondary school students

INTRODUCTION

Smoking has been identified as the single most important cause of preventable morbidity and premature death^[1]. The diseases which frequently occur among smokers include cardiovascular diseases, respiratory diseases and cancer^[2], such as coronary heart disease, lung cancer and tuberculosis^[3]. Globally, it is estimated that there are about 1 billion smokers and in 2014, smokers consumed 5.8 trillion cigarettes^[4]. Moreover, the World Health Organization (WHO)

estimates that annually 6 million people are killed by tobacco-related illnesses. Over 90% of these deaths are caused directly by tobacco use, whilst about 10% are the result of non-smokers being exposed to secondhand smoke^[5]. If current trends continue, it is projected that by 2030, tobacco will be responsible for more than 8 million deaths each year and 80% of these premature deaths will be among people living in low and middle income countries^[6], while rates of smoking have leveled off or declined in the developed world^[7].

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With regard to Arab and East Mediterranean countries, the WHO has reported a wide variation in the prevalence of smoking among young people: 7% in Oman, 18% in Kuwait, 23% in Iraq, 25% in Saudi Arabia and Jordan, 31% in Syrian Arab Republic, 42.5% in Turkey, 43% in Yemen and 53% in Lebanon^[8]. In Sudan, it has been estimated that the prevalence of cigarette smoking in adults is 24% in 2009, according to a WHO report published in 2010. However, the prevalence rates of smoking among young people is 13.7%^[9-10].

The results of epidemiological studies have identified smoking as a behavior learnt and initiated during adolescence and those who did not smoke during adolescence were unlikely to initiate smoking during their adulthood^[11]. The earlier the individual initiated smoking, the higher the likelihood of being inflicted by diseases related to smoking. In addition, adolescents who smoked were more likely to be involved in other high-risk behaviors^[12].

Previous studies of smoking among young people identified that an individual's relationships with others and environmental factors influenced smoking behavior among teenagers. Intrapersonal factors associated with adolescent smoking include lower levels of knowledge on hazards of smoking^[13], positive attitudes towards smoking and low self-esteem^[14], perceived high smoking prevalence among peers, as well as perceived positive reactions of parents and society towards smoking^[15]. In contrast, having best friends and family members who smoked, perceived less cordial family relationship, unsatisfactory academic achievements, perceived lower socio-economic status and lower status in school were the associated interpersonal and environmental factors of smoking behavior among adolescents^[11].

While some studies of adolescent smoking have been conducted in Sudan, only a few investigated the smoking behavior among young people in detail. Identifying the factors associated with smoking will support health authorities in designing the appropriate measures to deal with increasing prevalence of smoking among adolescents in Sudan. The purpose of this study was to assess the prevalence of smoking and describe the smoking behavior among male students in secondary schools in Khartoum.

SUBJECTS AND METHODS

The study population comprised of secondary school students who were living in Khartoum. A descriptive, cross sectional study of 3,87,377 students distributed in 160 secondary schools (109 private and 51 governmental schools) in Khartoum were surveyed.

The study was approved by the University of Khartoum Research Ethics Committee and Ministry of Education. Three secondary schools were randomly

selected from each of the four administrative units, hence obtaining 12 schools randomly. The study sample was calculated using the following formula and was found to be 379 students^[16].

Sample selection

Students were chosen proportionately from each school in the study area. Systematic random sampling was used to select students from the school list of students made by the researcher prior to distribution of data collection tool, and so, one student was selected from every 10 students in the list. All students in these schools were invited to take part in the study. Permission to conduct the research in the selected schools was taken from school heads. Informed consent of students was implied by completing and returning the questionnaire.

Data collection

The research instrument used for this study was a pre-tested, structured questionnaire. Data was collected from students regarding socio-demographic characteristics, and smoking variables were constructed to estimate cigarette smoking prevalence, smoker behavior and types of smoking products used. Data was also collected on the knowledge level related to attitude of students towards smoker. In addition, the data for the study was collected by twelve interviewers who were trained to conduct face-to-face interviews.

Statistical analysis

In order to meet the study objectives, the data obtained from the research instrument was analyzed. Depending on the nature of the variables, descriptive statistics were used to tabulate and describe the data (frequency distribution, percentages, means and standard deviations), and inferential statistics (Chi-Square tests) was used to examine the association between categorical variables. SPSS 20.0 was used to analyze the collected data.

RESULTS

Socio-demographic characteristics of students

A total of 379 students completed the questionnaire. From the 379 respondents, 267 (96.8%) were of the age 16 - 17 years, of which 22 (3.2%) were in the age of 18 - 19 years with a mean age of (17.5 ± 1.2 years). Three hundred and fifty five of the respondents (93.7%) were living in their family house, while 24 (6.3%) were living in their relatives' house. Relating to the class level, 150 (39.6%) of the total respondents were in third-year, 120 (31.7%) were in second-year and 109 (28.8%) students were in first-year.

A majority (65.9%) of the respondents had a monthly income ranging from 250 to 1000 Sudanese pounds (SP). While most of the students (88.9%) had a

per diem less than 10 SP, 5% had a per diem between 10 – 15 SP, and 6.1% had a per diem more than 15 SP and their family size was 5.2 ± 1.4 . However, a majority of the respondents' parents had formal education (father: 94.5% and mother: 91.6%). Table 1 shows that the prevalence of smokers among students was 12.9%, most of them (75.5%) were mainly cigarette smokers, while 16.3% were cannabis smokers, 6.1% were marijuana smokers and a substantial proportion (2.1%) of students combined different smoking methods. Of

Table 1: Behavioral factors related to smoking among secondary school students in Khartoum state, north Sudan (n = 379)

Smoking behavior	No. of students	%
Smoker	49	12.9
First trial to smoke	55	16.7
Cigarette	37	75.5
Marijuana	3	6.1
Cannabis	8	16.3
All types	1	2.1
Number of cigarettes smoked per day		
1 - 5	41	83.8
6 - 10	4	8.1
> 10	4	8.1
Source of cigarettes		
Bought themselves	25	51
Friends	14	28.6
Family members	10	20.4
Smoking members among family		
Father	74	19.5
Mother	4	1.1
Brother	48	12.7
All family members	2	0.5
None of the above	251	66.2
The period of trying smoking		
Pre-school	3	5.5
Primary school	27	54.5
Secondary schools	20	40

Table 2: Knowledge and attitude among students towards smoking (n = 379)

Variables	No. of students	%
Attitude towards female smokers		
Negative attitude	371	97.9
Positive attitude	8	2.1
Attitude towards male smokers		
Negative attitude	358	94.5
Positive attitude	21	5.5
Readiness to quit smoking (n = 49)		
Yes	48	98
No	1	2
Reasons behind students' supporting rules preventing smoking at public places		
Protect others	329	90.6
Maintain social norms	34	9.4
Factors that lead others to smoke		
Social	79	21
Economic	12	3.2
Psychological	287	75.8
Possibility of controlling smoking		
Rising awareness	356	93.9
Enforcement of laws and regulations	209	58.6
Others (Increase the cigarette price to reduce the rate of smokers)	141	39.5
Perception about smoking benefit	7	1.9
Existence of smoking benefits	18	4.7

the students who smoke, 54.5%, 40% and 5.5% started smoking during primary school, secondary school and pre-school respectively.

Regarding the number of cigarettes smoked per day, it was found that 83.8% of students were regularly smoking one to five times per day. The highest proportion (42.9%) claimed smoking was due to friends participation, followed by first trial (28.6%), imitation (12.2%), anxiety (10.2%) and independency (6.1%) (Fig 1). Also, students that reported having

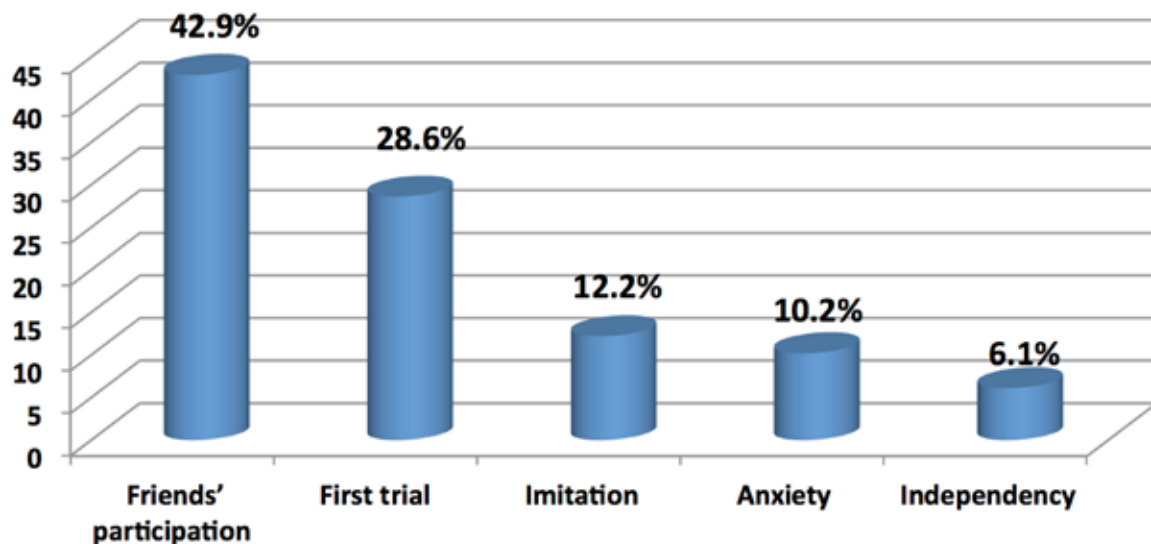


Fig 1: Reasons why students started smoking

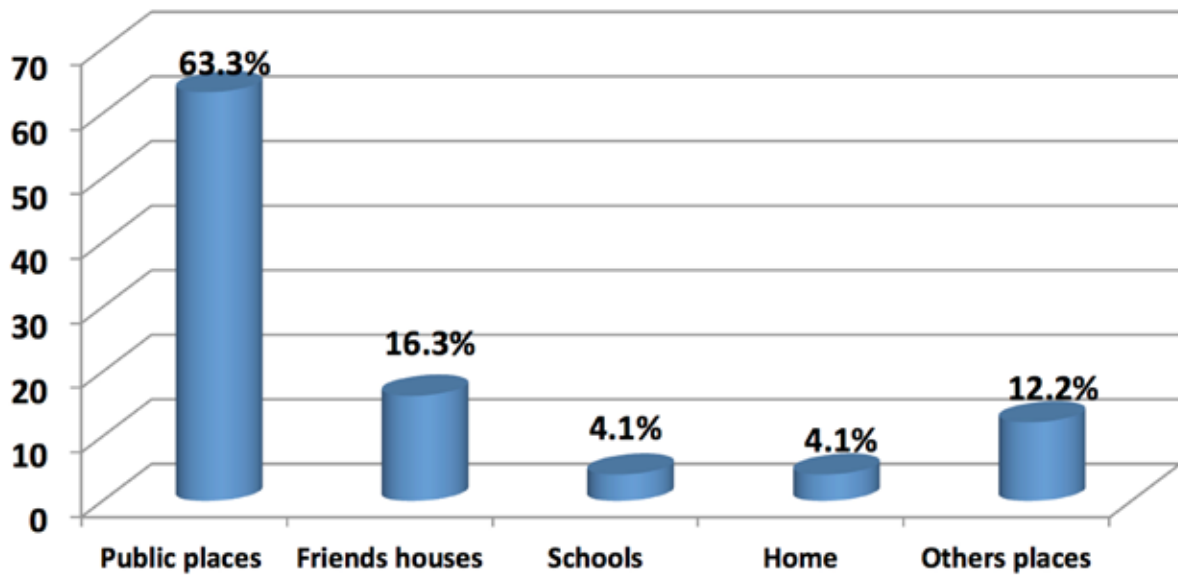


Fig 2: Places where students smoke

smoking members in their families included 74 with fathers who smoke (19.5%), 48 with brothers who smoke (12.7%), 4 with mothers who smoke (1.1%), and 1 who had all family members that smoked (0.5%).

In relation to the source of cigarettes, 25 (51%) of the students bought it by themselves, and only 14 (28.6%) and 10 (20.4%) got it directly from friends or one of their family members, respectively. However, regarding the place of smoking, the majority of the smokers reported that they smoked in public places (63.3%), followed by friends' houses (28.6%), and other places (12.2%),

while both schools and homes were not considered as good places for smoking (4.1%) (Fig 2). Table 2 shows that there is a negative attitude towards female smokers. A similar attitude was reported among study subjects regarding male smokers. Unfortunately, 5.5% of the respondents had positive attitude towards male smoking. Forty eight (98%) of the smoking students wanted to quit smoking. The most important reason that made them ready to quit smoking was to save their health (64.6%), followed by family wishes (20.8%) and to save money (8.3%) (Fig 3).

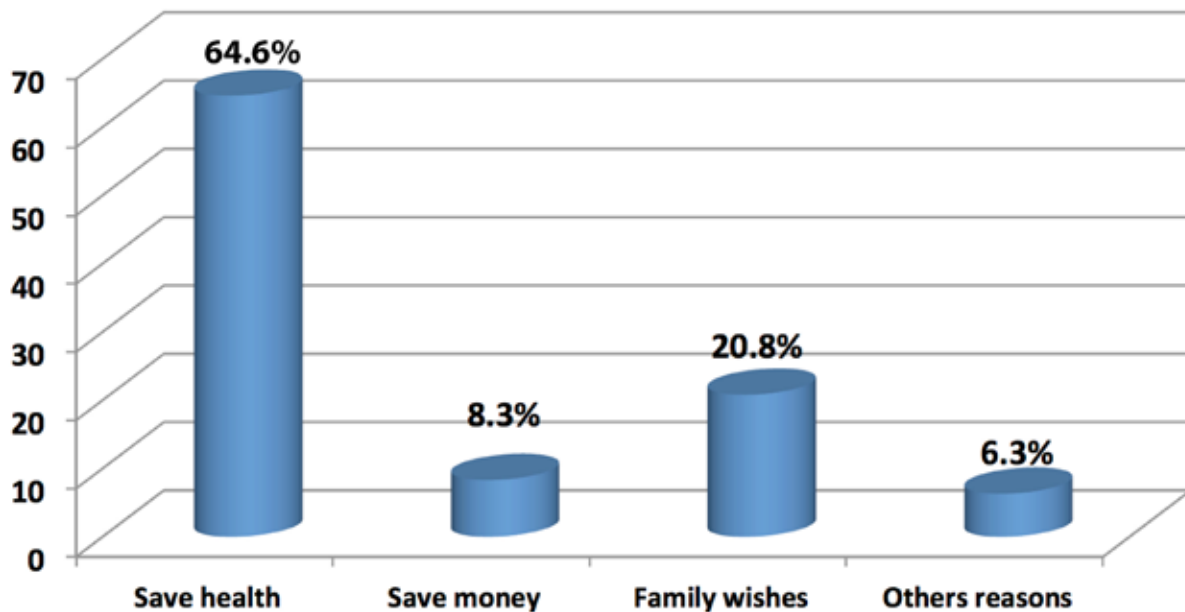


Fig 3: Reasons why students are ready to quit smoking

Three hundred and sixty-three (95.8%) of all respondents supported the rule that prevented smoking at public places, because they knew that this would protect others (90.6%) and maintain social norms (9.4%) respectively. Majority of the respondents reported that the factors that lead others to smoke was stress or psychological (75.8%), social (21%) and economic (3.2%).

The respondents suggested a list of strategies for smoking control. These suggestions included implementing health education programmes (58.6%), enforcement of laws and regulations (39.5%) and increasing the cigarette price to reduce the rate of smokers (1.9%).

The smokers reported that smoking has different types of benefits. These benefits include becoming more social, innovative and happy (Fig 4).

Table 3 shows socio-demographic characteristics significantly associated with smoking among school

students. The prevalence of smoking was higher among elder students (11.6%) than in younger students (1.3%), (Odds ratio (OR) = 1.12; 95% confidence interval (CI): 1.03 – 1.19), $p < 0.03$

The prevalence of smoking was higher among students in third-year secondary schools (6.9%) than among students in first year (1.2%) and second year (4.8%), ($p < 0.010$).

Moreover, students who had a smoking person in his family were significantly more likely to become a smoker (8.2%) than a student who came from a smoke-free home (4.7%) (OR = 4.14; 95% CI: 2.21 - 7.75).

However, significant associations were observed between students family size, monthly income and students per diem with the smoker status ($p < 0.05$), while the parents' education level and place of residence were not significant factors associated with their children's smoking habits ($p > 0.05$).

Table 3: The associations between socio-demographic characteristics and smoking among secondary school students (n = 379)

Characteristics	Smoking Status		p-value	OR	95% CI	Chi square value
	Smoker n (%)	Non-smoker n (%)				
Age						
16-17 year	5 (1.3)	80 (21.1)	0.03	1.12	1.03 - 1.19	4.428
18-19 year	44 (11.6)	250 (65.9)				
Class level						
First-year secondary	7 (1.8)	102 (26.9)	0.01	-	-	6.532
Second-year secondary	16 (4.2)	104 (27.4)				
Third-year secondary	26 (6.9)	124 (32.7)				
Place of Residence						
Family house	46 (12.1)	309 (81.6)	0.94	1.04	0.29 - 3.63	0.004
Relatives' house	3 (0.8)	21 (5.5)				
Family size						
< 3	2 (0.5)	10 (2.6)	0.002	-	-	9.321
3-6	32 (8.4)	136 (35.9)				
>6	15 (4)	184 (48.5)				
Educational level of father						
Informal education	3 (0.7)	18 (4.8)	0.849	1.13	0.32 - 3.98	0.36
Formal education	46 (12.2)	312 (82.3)				
Educational level of mother						
Informal education	4 (1.1)	28 (7.4)	0.940	1.00	0.87 - 1.15	0.006
Formal education	45 (11.8)	302 (79.7)				
Monthly income (SDG)						
< 250	0	8 (2.1)	0.04	-	-	4.051
250 – 500	8 (2.1)	74 (19.5)				
501 – 1000	13 (3.4)	109 (28.8)				
>1000	28 (7.4)	139 (36.7)				
Students per diem						
<10	40 (10.6)	297 (78.4)	0.001	-	-	2.779
10-15	4 (1.1)	15 (4)				
>15	5 (1.3)	18 (4.7)				
Smoker among family member s						
Yes	31 (8.2)	97 (25.6)	0.001	4.14	2.21 - 7.75	21.9
No	18 (4.7)	233 (61.5)				

OR: Odds ratio; 95% CI: 95% confidence interval

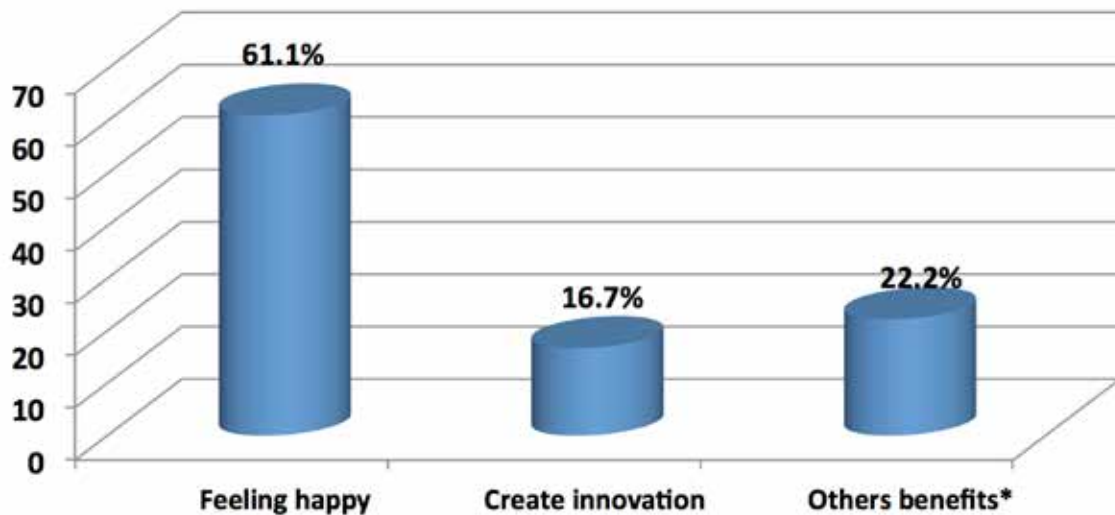


Fig 4: Perceptions about benefits of smoking

DISCUSSION

Smoking among young people is associated with a range of problems. This study aimed to assess the prevalence of smoking and describe the smoking behavior among male students in secondary schools in Khartoum. About 13% of the students in this study reported that they were smokers. This prevalence is relatively higher compared to results of other studies that have been carried out around the world, such as studies from United Kingdom and Kenya, where prevalence of smoking among secondary students were 12% and 12.5% respectively, and almost similar to that in Pakistan (13.7%)^[17-19]. Similarly high prevalence of cigarette smoking has been reported among secondary school students around the world. A study conducted in Malaysia, for example, found that 35.8% of students were smokers^[11] and another study conducted in Greece found that 18% of students were smokers^[20]. In Saudi Arabia, prevalence of cigarette smoking among secondary school students was 37% in Jeddah, 20.2% in Makkah and 15.2% in Madinah^[21-22,8]. However, the prevalence in Zimbabwe was found to be 37.8%^[23]. Furthermore, the WHO has reported a wide variation in the prevalence rates of smoking among young people in Eastern Mediterranean countries: 7% in Oman, 18% in Kuwait, 23% in Iraq, 25% in Saudi Arabia and Jordan, 31% in Syrian Arab Republic, 42.5% in Turkey, 43% in Yemen and 53% in Lebanon^[8].

This study also showed that among smokers, 75.5% of students smoked only cigarettes, 16.3% of them were cannabis smokers and 6.1% were marijuana smokers. According to the Centre for Disease Control, tobacco, marijuana and other substance abuse are gateway drugs and when younger children use them, they are often more likely to abuse cocaine, heroin

and other hallucinogens^[7]. This is enough evidence to encourage decision makers to increase efforts to prevent childhood use of cigarette and cannabis.

The results show that 42.9% of the students who were smokers claimed that the decision to begin smoking was due to influence of friends and family members, particularly fathers (19.5%), and brothers (12.7%). These results are consistent with other studies which have found that young people take up smoking largely due to peer pressure. In 2011, Amin *et al* in Al-Hassa found that smoking of close relatives and friends were statistically significant determinants of current smoking status among secondary school students^[24]. This indicates that smoking friends and parents play an important role in the increased risk of smoking among male secondary school students.

A majority (54.5%) of the smokers started smoking during primary school. This is similar to other studies done in Nigeria^[25]. This highlights that cigarette smoking habits started early in childhood and therefore efforts should be directed at preventing its occurrence in that stage itself.

Regarding the number of cigarettes smoked per day, it was found that 83.8% of students were regularly smoking one to five times per day. This proportion was higher than the 68.5% of students who smoked less than 5 cigarettes per day that was reported previously^[10]. Our results are also in contrast to a study conducted in Majmaah city by Al-ghaneem *et al*, wherein it was reported that 41.3% of the respondents smoked between 10 to 20 cigarettes per day^[8]. We conclude that since the study subjects smoked one to five times per day, they carried a higher risk of dying of ischemic heart disease and lung cancers as compared to non-smokers, as has been evident from the findings

of Bjartveit *et al*, whose study showed that consumers of 1 to 4 cigarettes per day have a 2.74 times higher risk of dying of ischemic heart diseases as compared to nonsmokers^[26].

With respect to attitudes towards male and female smoking, majority of the respondents had passive attitudes regarding male and female smoking (97.9% and 94.5%, respectively). This finding is consistent with Asghar *et al*, who found in 2012 that 95% of students had negative attitude towards cigarette smokers. Negative attitudes toward smoking will play a major role in reducing the uptake of smoking among young people. Many studies have shown that smoking is more common among young people who have tolerant attitudes toward smoking^[27].

Our results also showed that a majority of the smokers had a desire to quit smoking (98%) because they knew that cessation of smoking will improve their health (64.6%). These results were higher compared to the study conducted by Gadalla *et al*, who found that 50% of smokers had a desire to stop smoking. It is also higher than the finding of the study conducted in secondary school students at Jeddah (63.2%)^[22].

In this study, the respondents suggested a list of strategies for smoking control. These suggestions include raising awareness about health problems associated with smoking (58.6%), enforcement of laws and regulations (39.5%) and increasing the cigarette price to reduce the rate of smokers (1.9%). These suggestions are consistent with a previous study conducted by Al-Maimani, who recommended that health education and religious orientation should be the cornerstones for any organized tobacco control programs^[21]. Al-Maimani *et al* and Adeyeye recommended aggressive anti-smoking campaigns backed by effective legislation to reduce this trend^[28].

The results of this study demonstrated that the prevalence of smoking was higher among elder students (11.6%) than in younger students (1.3%, $p < 0.001$). Additionally, the present study reveals that third-year secondary schools (6.9%) had a significantly higher prevalence of smoking than students in the first and second year (1.8% and 4.2% respectively, $p < 0.001$). Similar results in previous studies reported the smoking rate was significantly higher among upper secondary (9.1%) compared to 5.4% of lower secondary students^[29].

Moreover, a student who has a smoker in the family is significantly more liable to become a smoker (8.2%) than a student who came from smoking-free homes (4.7%). These findings were in agreement with those reported by Villanti^[30].

However, no significant associations were observed between fathers' and mothers' educational

level. This indicates that the level of education of the parents is not a predictor of smoking uptake among young people. This is in contrast with a general report of United States surgeons, where the authors reported that the level of education of the parents is a predictor of the uptake of smoking among the young^[7].

CONCLUSION

In conclusion, the prevalence of smoking was relatively high among secondary schools students (12.9%). This study demonstrated many factors which were associated with smoking among Sudanese secondary school students. To reduce the prevalence of smoking, intensive interventional measures should target parents, teachers and students, and should start as early as primary schools to empower students with skills to resist peer pressure.

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Original Article

Transthoracic Needle Aspiration Biopsy Experience of 162 Cases Operated for Non-Small Cell Lung Cancer

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ABSTRACT

Objectives: Computed tomography-guided percutaneous transthoracic needle biopsy (CT-TNB) is used for identifying lung lesions. In this study, we reviewed the diagnostic value of CT-TNB based on comparison of the preoperative and postoperative diagnosis of patients diagnosed using CT-TNB.

Design: Retrospective study

Setting: Thoracic Surgery Department of Kocaeli University Medical Faculty, Kocaeli, Turkey

Subjects: One hundred and sixty-two patients who underwent lung resection due to non-small cell lung cancer were examined between January 2010 and May 2016.

Intervention: CT-TNB

Main outcome measure(s): Concordance between diagnosis after CT-TNB and diagnosis after resection were determined based on tumour subtype, location, and size.

Results: Diagnostic values of CT-TNB were as follows: 78% adenocarcinoma, 83% squamous cell carcinoma, and 94% large cell carcinoma. Specificity-sensitivity values according to histopathological group were as follows: 76.62 to 80% for adenocarcinoma and squamous cell carcinoma, 79.84% to 93.93% for squamous cell carcinoma, and 50% to 94.37% for large cell carcinoma.

Conclusion: CT-TNB is a relatively safe and highly accurate method for evaluating lung nodules. The primary risk factors for complications from CT-TNB are the presence of emphysema on CT scan.

KEY WORDS: computed tomography, transthoracic, needle, biopsy

INTRODUCTION

Lung cancer is one of the deadliest types of cancer worldwide. The 5-year survival rate is approximately 50% because it is typically diagnosed at an advanced stage^[1]. Only 16% of lung cancer cases are diagnosed in the early stages^[1]. Using computed tomography (CT) guided percutaneous needle biopsy has become the most common histopathological diagnosis technique in lung cancer^[2,3]. Stage and localisation of the illness, as well as the age, performance, and respiration capacity of the patient, determine the treatment procedures. When these factors are considered, chemotherapy and radiotherapy are crucial for the treatment of lung cancer. Surgical treatment of lung cancer has a relatively low prevalence rate (20%). In operable lung cancer cases, histological examination can be more

detailed because whole tumour in the resected lung is examined directly by a histopathologist. Therefore, the diagnostic accuracy is quite high in these cases. However, in non-operable cases, the accuracy of diagnosis via minimally invasive methods must be reviewed according to the patient's response to treatment. In this study, we reviewed the diagnostic value of CT-guided transthoracic fine needle aspiration biopsy (CT-TNB) based on comparison of the preoperative and postoperative diagnosis of patients diagnosed using CT-TNB.

SUBJECTS AND METHODS

In this study, 162 patients who underwent lung resection due to non-small cell lung cancer at the Thoracic Surgery Department of Kocaeli University

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Medical Faculty were examined retrospectively between January 2010 and May 2016. A total of 146 (90.1%) cases were men and 16 (9.9%) were women. During the pre-operative stage, diagnosis was made based on CT-TNB. Lesions were classified according to size and location. Biopsy was performed using 16-detector CT (Activion 16-multislice CT; Toshiba Medical Systems Corp.) by interventional radiology. All biopsies were performed by the same clinician. A standard 15 cm, 22-gauge (G) needle was used for biopsy. Coagulation parameters (prothrombin time, partial thromboplastin time, bleeding time, platelets) of all patients were evaluated prior to biopsy. In 27 cases, extension of bleeding time due to aspirin usage was observed. Aspirin usage was ended 1 week before surgery and control coagulometric measurements were normal. Prior to this, patients were examined by positron emission tomography CT (PET-CT) and the most intense fludeoxyglucose (FDG) uptake areas of the lesion were determined. Additional examination of the patient's radiologic images was used to evaluate emphysematous lines in the lungs, the relationship of the lesion with the pulmonary arteries, the path of the needle, and the patient's position. The needle must not pass through the interlobar fissure or wide vascular areas. After determining the path of the needle, 3 - 5 ml of 1% lidocaine was injected subcutaneously into the tissue. CT-guided needles were then placed into the lesion. The same pathologist observed this process in all patients and evaluated whether the material was sufficient. Routinely, sufficient material was obtained in all cases after five to seven passes of transthoracic needle biopsy (TNB). Complications such as pneumothorax and haemorrhage were evaluated during the same stage.

A total of 137 (84.6%) patients diagnosed with lung cancer and who were suitable for the operation underwent anatomic resection (lobectomy, pneumonectomy). Segmentectomy or wedge resection was applied to 13 (8%) patients. Wide resection (chest wall/diaphragm resection) was applied to 12 (7.4%) patients. Concordance between diagnosis after CT-TNB and diagnosis after resection were determined based on tumour subtype, location, and size.

Statistical analysis was performed using SPSS software (ver. 20.0; SPSS Inc., Chicago, IL, USA). Normality of distribution of the data was evaluated using the Kolmogorov-Smirnov Test. Numerical variables showing normal distribution are shown as means \pm standard deviation. Numerical variables not showing normal distribution are shown as median (25th - 75th percentile). Categorical variables are shown as frequencies (percentages). The effective magnitude

of independent variables/risk factors, which are effective on the variance of the dependent variable, was calculated based on logistic regression analysis (related-samples Kendall's coefficient of concordance test). The relationships among categorical variables were evaluated using chi-square analysis. P-value < 0.05 was considered significant.

RESULTS

In our study, there were 146 (90.1%) male and 16 (9.9%) female patients. The average age was 61.02 ± 7.38 years (60.95 ± 7.37 and 61.63 ± 8.80 years for men and women, respectively). There was no statistical difference between the male and female patients in terms of age distribution ($p = 0.73$). When lesions were evaluated according to location, 56 (34.6%) were in the right lung upper lobe, 8 (4.9%) were in the right middle lobe, 37 (22.8%) were in the right lower lobe, 32 (19.8%) were in the left upper lobe, and 29 (17.9%) were in the left lower lobe. When classified according to size, there were 88 (53.8%) lesions ranging from 0 - 3 cm, 53 (32.7%) lesions ranging from 3 - 5 cm, and 21 (13%) lesions measuring > 5 cm. One hundred and two (62.95%) lesions were located peripherally and 60 (37.5%) lesions were located centrally. Both groups were included in logistic regression analysis between localizations. In 45 (27.77%) patients, procedure-related complications were observed; 34 (21%) cases had pneumothorax and 11 (6.79%) had intraparenchymal haemorrhages (Fig 1). Twenty-nine (17.9%) patients with pneumothorax underwent observation treatment. A total of 11 patients (6.79%) were observed in the emergency department for 6 hours; they were discharged after examined control

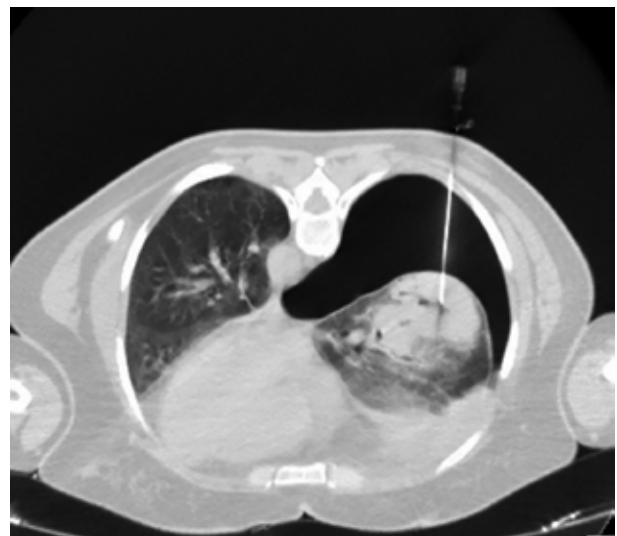


Fig 1: Pneumothorax on the CT scan performed during the transthoracic needle biopsy

Table 1: Histological patterns observed on CT-TNB and post-operative and diagnostic values of CT- TNB

Pathology	Adenocarcinoma n (%)	Squamous ca. n (%)	Adenosquamous n (%)	Large cell ca. n (%)	Non-specific n (%)
CT-TNB	85 (52.5)	33 (20.4)	0	2 (1.2)	42 (25.9)
Post-operative	86 (53.1)	57 (35.2)	3 (1.9)	10 (6.2)	6 (3.7)
Diagnostic values of CT-TNB	78%	83%	0	94%	0

ca: carcinoma

chest radiography. A total of 18 (11%) patients were followed in the Department of Thoracic Surgery with oxygen therapy for 2 - 5 days (average: 2.68 ± 0.76 days). Tube thoracostomy was used in five (3%) patients who were followed for 3 - 7 days (average: 3.80 ± 0.95 days). The patients with intraparenchymal hemorrhages were followed up for 24 hours in thoracic surgery clinic. Chest x-ray and blood count were assessed as normal and the patients were discharged.

After CT-TNB, patients were diagnosed as follows: 85 (52.5%) with adenocarcinoma, 33 (20.4%) with squamous cell carcinoma, 42 (25.9%) were non-diagnostic, and 2 (1.2%) with large cell carcinoma. During the post-operative stage, after histopathological examination of resection material, cases were evaluated as follows: 86 (53.1%) with adenocarcinoma, 57 (35.2%) with squamous cell carcinoma, 10 (6.2%) with large cell carcinoma, 3 (1.9%) with adenosquamous cell carcinoma, and 6 (3.7%) with non-specific lesions (Table 1).

In the 86 post-operative adenocarcinoma cases, distinctions were made as follows: 30 (35%) acinar, 22 (25%) solid, 18 (21%) lepidic, 5 (6%) mucinous, 3 (4%) papillary, and 8 (10%) others (Table 2). None of the adenocarcinoma sub-patterns were determined based on CT-TNB.

Although sufficient material was observed in

Table 2: Histological subtypes of adenocarcinoma

Subtypes of adenocarcinoma	Number of cases n (%)
Acinar	30 (35)
Solid	22 (25)
Lepidic	18 (21)
Mucinous	5 (6)
Papillary	3 (4)
Others	8 (10)
TOTAL	86 (100)

CT-TNB-applied cases based on histopathological examination, only 120 (75%) of the cases could be diagnosed. When CT-TNB and resection material were evaluated together, diagnostic values of CT-TNB were as follows: 78% adenocarcinoma, 83% squamous cell carcinoma, and 94% large cell carcinoma

(Table 1). Specificity-sensitivity values according to histopathological group were as follows: 76.62 - 80% for adenocarcinoma and squamous cell carcinoma, 79.84 - 93.93% for squamous cell carcinoma, and 50% to 94.37% for large cell carcinoma. After logistic regression analysis, lesion size and localisation did not affect the concordance between CT-TNB and pathology ($p = 0.0032$).

DISCUSSION

There are various diagnostic techniques for lung lesions. Location and stage of the lesion, as well as the patient's overall condition, are the most important for determining the diagnostic method. Sputum cytology, bronchoscopy, CT-TNB and surgical sampling are the most common diagnostic methods. Although sputum cytology is an easy and inexpensive diagnostic method, it is not reliable due to its high false-negative rate^[1]. During bronchoscopy, central lesions are commonly found; however, peripheral and pleural lesions cannot be diagnosed with this technique^[4]. Surgical diagnosis is preferred in operable patients, but the prevalence rate of surgery is only 20% in lung cancer cases^[5]. Transthoracic biopsy is one of the most common diagnostic methods because it has the largest patient spectrum and a high accuracy diagnosis rate.

Although the development of CT has allowed more effective identification of smaller lesions, histological sampling is required to determine whether lesions are malignant or benign, and primary or secondary. In particular, determination of histological subtype is important for treatment planning. Biopsy techniques with a high diagnosis rate and low complication rate are considered to be optimal^[6]. In these respects, it is clear that the value of transthoracic biopsy is quite high. There is no specific contraindication for CT-TNB, but coagulation disorders must be identified a priori^[7]. In all cases, coagulometric measurements were performed a priori and no medicine was administered to patients with anticoagulant usage. CT-TNB is applied only to one functional lung. Although chronic respiratory failure, pulmonary arterial hypertension, cardiac insufficiency, and severe emphysema are only relative contraindications, the complication risk may increase with their presence. Transthoracic

biopsy complications are rarely seen; from the most to least frequent, these include pneumothorax, haemorrhage, and chest pain. Pneumothorax is the most common complication, seen in 12% to 45% of cases^[8]. Repeated biopsies, emphysematous lung and deep lesion localisation increase the pneumothorax risk. The pneumothorax rate in our cases was 21% and tube thoracostomy was applied to 3% of these cases. After CT-TNB, intraparenchymal haemorrhage rates varied from 4 to 27%^[8]. In our study, intraparenchymal haemorrhage was observed in 11 cases (6.79%). No additional surgical intervention was required.

The probability of malignant, 5 mm lesions in the lung was 0 - 1%. In such cases, follow-up is suggested. In a previous study, the malignancy potential for 5 - 10 mm lesions was 6 - 28% and 64% - 82% for 20 mm-sized lesions^[9]. Since the malignancy potential of small lesions is relatively low, surgery is not required to limit the complication risk. In patients with high malignancy potential, exclusion of small cell lung cancer is very important. In addition, CT-TNB is a minimally invasive method that, combined with histopathological examination, provides rapid results. The accuracy of CT-TNB in the diagnosis of pulmonary malignancies is 80 - 95%^[10]. Pneumothorax and the size of the lesion are both factors affecting false-negative diagnoses. Large lesion size increases the false-negative rate^[11] because, in wide consolidation, it is difficult to distinguish malignant cells within the primary lesion from atelectasis and inflamed areas^[11]. In addition, the true diagnosis rate of CT-TNB applied to subsolid lesions was lower than that for completely solid lesions^[12]. Thus, pathological evaluations of adenocarcinomas that are identified as subsolid lesion in thoracic BT can be inaccurate. In our study, when CT-TNB and resection material were evaluated together in a similar manner, the diagnostic value for adenocarcinoma was 78%. For squamous cell carcinoma, this value was 83%, while for large cell carcinoma it was 94%. Specificity-sensitivity values according to histopathological group were as follows: 76.62 - 80% for adenocarcinoma, 79.84 - 93.93% for squamous cell carcinoma, and 50 - 94.37% for large cell carcinoma. In recent studies, PET-CT was shown to play an important role in the determination of biopsy area in lung lesions, and also increases the diagnostic value^[13]. In our cases, PET-CT evaluation was conducted prior to the CT-TNB and biopsy areas were determined according to this evaluation. The presence of a pathologist in the team during biopsy to determine whether sufficient material has been obtained decreases the number of procedures required^[14]. In our cases, a pathologist was present during the biopsies.

In a classification system introduced in 2011,

adenocarcinomas were classified according to the dominant histological pattern to allow target-specific, personalised treatments. Epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and Kirsten ras oncogene (KRAS) genetic mutations are often seen in adenocarcinomas. At this time, targeted inhibitors are used against EGFR and ALK mutations. Some studies show that CT-TNB material is sufficient for such genetic examinations^[15,16]. To obtain the material necessary to determine adenocarcinoma subtype, the number of CT-TNB operations in the same clinic need to be increased. However, any such increase enhances the risk of complications. Of our 86 post-operative adenocarcinoma cases, 30 (35%) were acinar, 22 (25%) were solid, 18 (21%) were lepidic, 5 (6%) were mucinous, 3 (4%) were papillary, and 8 (10%) were "other" tumours. None were distinguished based on CT-TNB. Number of passes has a significant effect on diagnosis because obtaining insufficient material reduces diagnostic rate. According to our experience, if there is no pathologist in research team, at least seven passes of TNB must be performed to obtain sufficient material. In our cases, we performed CT-TNB within the shortest time possible and minimised the number of passes to decrease the complication rate. Thus, when the pathologist on our team obtained sufficient material for malignancy distinction, the process was considered complete. While the same approach is used by many clinics, the determination rate of CT-TNB subtype is relatively low, since in studies performed using currently available treatment options, distinction of adenocarcinoma subtype makes no significant contribution to the survival time.

CONCLUSION

Advanced treatment protocols require performance of CT-TNB to a higher level. In particular, as methods such as PET-CT and CT continue to improve, the diagnostic value of CT-TNB will increase.

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Original Article

Comparison between the Effect of Ear Plug and Music in Reducing Anxiety in Patients Undergoing Elective Cesarean Section under Spinal Anesthesia

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ABSTRACT

Objectives: To compare the effect of ear plug and music in reducing anxiety in patients undergoing elective cesarean section under spinal anesthesia

Design: A randomized, single-blind, prospective study

Setting: Imam Reza Hospital, Kermanshah, Iran

Subjects: Ninety pregnant women undergoing elective caesarian section using spinal anesthesia

Intervention: The subjects were randomly divided into three groups: music group, ear plug group and control group, each including 30 individuals. Spielberger State-Trait Anxiety Inventory (STAI) was used to evaluate the individuals' anxiety before and after the intervention. SPSS version 20 was used to analyze the data. One-way analysis of variance, Chi square, and paired samples t-test were used to compare the data.

Main outcome measure(s): Anxiety

Results: There were significant differences between the mean

scores of the STAI questionnaire in music (21.83 ± 11.9 vs. 13 ± 8.02) and control groups (24.4 ± 11.89 vs. 16.6 ± 8.14) pre and post-test ($p = 0.001$) but not in ear plug group ($p = 0.327$). There were significant differences between the mean scores of the STAI questionnaire in music (21.83 ± 11.9 vs. 13 ± 8.02) and control (24.4 ± 11.89 vs. 16.6 ± 8.14) groups pre and post-test ($p = 0.001$) in parity I group. For individuals with under diploma level of education, there were significant differences between the mean scores of the STAI questionnaire in music (21.23 ± 11.78 vs. 13.55 ± 8.17) and control (24.96 ± 11.61 vs. 16.17 ± 7.45) groups pre and post-test ($p < 0.05$). For individuals under 30 years of age, there were significant differences between the mean scores of the STAI questionnaire in music group pre (21.60 ± 12.51) and post-test (13.30 ± 7.66) ($p < 0.05$).

Conclusions: Only music has effect on reducing anxiety in parity I group and those with under diploma level of education.

KEY WORDS: anxiety, cesarean section, earplug, music, spinal anesthesia

INTRODUCTION

Patients who are waiting for surgical procedures normally experience anxiety due to the risk of unpredictable events that may threaten their health. High levels of anxiety lead to some negative outcomes including elevated blood pressure, increased levels of cortisol, elevated heart rate, slower wound healing, reduced immune response, and greater risk of infection^[1]. High anxiety levels could have a negative effect on the induction

of anaesthesia and may hinder postoperative recovery^[1,2]. Sedatives or antianxiety drugs are normally administered before surgery to decrease the anxiety of patients, although, sedatives usually have adverse effects including sleepiness and respiratory depression, and may possibly interfere with anesthetic agents and can prolong the recovery and discharge of patients^[3]. Therefore, to reduce the anxiety of surgery, more attention is paid to non-pharmacological interventions^[3,4].

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Cesarean section (CS) is one of the most prevalent surgical procedures done on pregnant women, and spinal anesthesia is the favored method of anesthesia due to lower risk and better benefits for both mother and fetus. Previous studies have shown that the anxiety of being awake during surgery is one of the main reasons for choosing general anesthesia^[5,6]. Some studies have evaluated the effect of playing music and ear plug before or during the surgery on patients' anxiety. Kushnir *et al*'s study has assessed the effect of listening to favorite music just before the cesarean and found it helpful in reducing anxiety^[7]. In another study by Li *et al* on women undergoing cesarean delivery, it was demonstrated that preoperative music intervention can decrease anxiety and pain^[8]. In a study by Gonano *et al*, in orthopedic surgery after sedation with propofol, the case group used earplug and the result showed that the ear plug reduced the intraoperative awareness with recall^[9]. Ni *et al* revealed that music reduced preoperative anxiety and improved the physiological parameters in day surgery patients^[10].

No specific premedication is accepted widely in spinal anesthesia, while the anesthesiologist is required to control the anxiety of patients during surgery. Given the risk of sedation and its adverse effects on mother and child except in certain limited cases, mothers do not receive any medical treatment during the cesarean section. This condition in case of high levels of anxiety may lead to rejection of spinal anesthesia, while spinal anesthesia can be helpful for patients^[11]. In a study by Berbel *et al*, the effects of diazepam and music were evaluated in preoperative patients' anxiety and it was shown that the effect of music and diazepam were similar in patients' anxiety^[12].

In previous studies, the pre-operation interview and visit, spousal participation in delivery, preparing the pamphlet about the surgery, playing music during surgery and using ear plug were used to decrease the anxiety, which showed different results. Therefore, more studies in this area are needed. In the present study, we compared the effect of ear plug and music in reducing anxiety in patients undergoing elective cesarean section under spinal anesthesia.

SUBJECTS AND METHODS

This is a randomized, single-blinded, prospective study which was held in Imam Reza Hospital of Kermanshah, Iran. The ethical principles were considered according to the Declaration of Helsinki. All patients were aware of the study and written informed consent was obtained from the patients. The inclusion criterion was ASA (American Society for Anesthesiology) classes I and II pregnant women who were candidates for elective cesarean section for

delivery and the exclusion criteria were the history of psychological problems, a history of psychotropic drug use, hearing problems, and dissatisfaction about participation in the study. Ninety pregnant women were randomly divided into 3 groups: music group, ear plug group and control group, each including 30 individuals. The sample size was determined with the confidence interval of 95% and the power of 90%.

Speilberger State-Trait Anxiety Inventory (STAI) was used to evaluate the individuals' anxiety and to assess how they react to mental pressure. The test was designed by Spielberger *et al* and contains 40 questions, among which 20 are related to state anxiety which is influenced by the situation and the other 20 are related to trait anxiety that is influenced by the current feeling of the subjects. The test retest reliability of the test was from $r = 0.73$ to $r = 0.86$ with an acceptable internal consistency of Cronbach's $\alpha = 0.89$ ^[13]. Aezimi and Zarghami defined the internal consistency of the test which was Cronbach's $\alpha = 0.9$ ^[14].

Dural puncture in the L4/L5 intervertebral space in sitting position was performed for all three groups using a 25-gauge needle. After ensuring the correct location of the puncture, spinal anesthesia with a standard dose of bupivacaine 0.5% was performed.

The control group received routine medical care. In the ear plug group, in addition to routine medical care after anesthesia, ear plug (ACU Life-ear plug with the noise reduction rating of 30 db) was used for individuals.

In the music group, in addition to routine medical care, through a headphone the "Motivation" piece of Doctor Arand Ashtian, a sedative musical piece of the Iranian Music Therapy Association, was played during the surgery.

Headphones or ear plugs were applied after dural puncture and went on until the end of surgery and was only discontinued before starting surgery for evaluation of anxiety.

The anxiety levels of the individuals were assessed before and after the surgery using the STAI questionnaire.

Statistical Analysis

SPSS version 20 was used to analyze the data. Values are significant at $p < 0.05$. One-way analysis of variance (ANOVA), Chi square, and paired samples t-test were used to compare the data.

RESULTS

The demographic features of the patients are demonstrated in Table 1. There were no significant differences between the age in the three groups ($p = 0.068$). In addition, no significant difference were seen between the level of education in the three

Table 1: The demographic features of the patients

Variables	Groups			p-value
	Music (n = 30)	Ear Plug (n = 30)	Control (n = 30)	
Age (years, mean ± SD)	27.1 ± 4.94	30.17 ± 8.11	26.6 ± 5.59	0.068
Education (n(%))				0.119
Under Diploma	22 (73.3)	28 (93.3)	24 (80)	
Diploma to Bachelor Degree	8 (26.7)	2 (6.7)	6 (20)	
Parity				0.038
I	18 (60)	15 (50)	25 (83.3)	
II	8 (26.7)	6 (20)	3 (10)	
III	4 (13.3)	9 (30)	2 (6.7)	

groups ($p = 0.119$). Although a significant difference was observed in parity among groups ($p = 0.038$), the difference between music and control group ($p = 0.135$) and music and ear plug group ($p = 0.326$) were not significant.

According to Table 2, there were significant differences between the mean scores of the STAI questionnaire in music and control groups pre and post-test ($p = 0.001$), but no significant difference were seen in ear plug group ($p = 0.327$), which means that this method had no significant effect on score reduction post-test. Although the result of one-way ANOVA showed no significant difference between the scores in the three groups, the result of post-test score showed a difference among the groups. The result of Tukey test revealed that the difference was related to the difference between the scores of music and ear plug ($p = 0.007$), while there was no significant difference between the mean score of control group and the two other groups.

Table 2: The mean scores of the STAI questionnaire

Variables	Groups (mean ± SD)		
	Music (n = 30)	Ear Plug (n = 30)	Control (n = 30)
Pre-Test	21.83 ± 11.9	22.63 ± 12.13	24.4 ± 11.89
Post-Test	13 ± 8.02	20.17 ± 10.38	16.6 ± 8.14
p-value	0.001	0.327	0.001

For parity I, Table 3 shows that there were significant differences between the mean scores of the STAI questionnaire in music and control groups pre and post-test ($p = 0.001$) but no significant difference was seen in ear plug group ($p = 0.834$). Although the result of one-way ANOVA showed no significant difference between the scores in three groups, the result of post-test score showed a difference among groups. The result of Tukey test revealed that the difference was related to the difference between the scores of music and ear plug ($p = 0.002$), while there was no significant difference between the mean score of control group and the two other groups.

Table 3: the mean scores of the STAI questionnaire with regard to parity

Variables	Groups (mean ± SD)		
	Music (n = 30)	Ear Plug (n = 30)	Control (n = 30)
Parity I			
Pre-Test	21.83 ± 11.9	22.63 ± 12.13	24.4 ± 11.89
Post-Test	13 ± 8.02	20.17 ± 10.38	16.6 ± 8.14
p-value	0.001	0.327	0.001
Parity II and III			
Pre-Test	21.83 ± 13.04	24 ± 13.33	22.2 ± 8.5
Post-Test	14.83 ± 6.87	18.27 ± 9.02	12.6 ± 8.76
p-value	0.001	0.089	0.129

For parity II and III, Table 3 shows that in contrast to parity I, no significant difference was seen between the mean scores of the STAI questionnaire in any of the groups pre and post-test ($p > 0.05$).

The results demonstrated that only music can effect score reduction and this effect is only significant for parity I group.

Table 4 demonstrates that for individuals with under diploma level of education, there were significant differences between the mean scores of the STAI questionnaire in music and control groups pre and post-test ($p < 0.05$) but no significant difference were seen in ear plug group ($p = 0.358$). Although the result of one-way ANOVA showed no significant

Table 4: The mean Scores of the STAI questionnaire with regard to the educational level

Variables	Groups (mean ± SD)		
	Music (n = 30)	Ear Plug (n = 30)	Control (n = 30)
Under Diploma			
Pre-Test	21.23 ± 11.78	23.25 ± 11.73	24.96 ± 11.61
Post-Test	13.55 ± 8.17	20.96 ± 10.16	16.17 ± 7.45
p-value	0.005	0.358	0.002
Diploma or More			
Pre-Test	23.5 ± 12.91	14 ± 19.8	22.17 ± 13.89
Post-Test	11.5 ± 7.91	9 ± 8.48	18.33 ± 11.16
p-value	0.094	0.844	0.368

difference between the scores in three groups in pre-test, the result of post-test score showed a difference among groups. The result of Tukey test revealed that the difference was related to the difference between the scores of music and ear plug ($p = 0.004$).

For educational levels ranging from diploma to bachelor degree, Table 4 shows that in contrast to under diploma, no significant difference was seen between the mean scores of the STAI questionnaire in any of the groups, pre and post-test ($p > 0.05$).

The results show that only music is effective in score reduction and this effect is significant in under diploma individuals.

Table 5 demonstrates that for individuals under 30 years of age, there were significant differences between the mean scores of the STAI questionnaire in music group pre and post-test ($p < 0.05$) but no significant difference were seen in ear plug group and control groups ($p > 0.05$). Although the result of one-way ANOVA showed no significant difference between the scores in three groups pre-test, the result of post-test score showed difference among groups. The result of Tukey test revealed that the difference was related to the difference between the scores of music and ear plug ($p < 0.001$), and control and ear plug ($p = 0.004$).

Table 5: The mean scores of the STAI questionnaire with regard to the age

Variables	Groups (mean \pm SD)		
	Music (n = 30)	Ear Plug (n = 30)	Control (n = 30)
Age < 30 (years)			
Pre-Test	21.60 \pm 12.51	26.60 \pm 12.04	21.28 \pm 12.10
Post-Test	13.30 \pm 7.66	24.87 \pm 10.19	16.06 \pm 7.23
p-value	0.017	0.673	0.091
Age \geq 30 (years)			
Pre-Test	22.30 \pm 11.23	18.67 \pm 11.24	29.08 \pm 10.33
Post-Test	12.40 \pm 9.09	15.47 \pm 8.48	17.42 \pm 9.63
p-value	0.020	0.306	0.003

In patients \geq 30 years old, there was a significant difference seen between the scores of pre- and post-test in music and control group ($p < 0.05$) but no difference was seen by ANOVA test in between the scores in the three groups.

DISCUSSION

Although it is proved that spinal anesthesia in cesarean section is beneficial for mother and fetus, the awake situation of the pregnant women increases the anxiety of subjects and they may tend to have general anesthesia. In the present study, we tried to assess the effect of music and using ear plug on reducing the anxiety of pregnant women who are candidates for elective cesarean section using spinal anesthesia.

The result of the present study revealed that music significantly reduces the anxiety of pregnant women. The result of this study was consistent with some other studies. Koelsch *et al* in 2011 have evaluated the effect of music on anxiety during surgery in 40 individuals who underwent spinal anesthesia and have found that it reduced anxiety and sedative requirements^[15]. In a study by Lee *et al* in 2011, different music playing instruments were assessed for reducing preoperative anxiety. One hundred and sixty seven patients were randomly divided into broadcast, headphone and control group. The anxiety was measured using visual analog scale and heart rate variability. It was revealed that both headphones and broadcast music were effective in reducing the anxiety of patients^[16]. Another study by Cooke *et al* on the effect of music on day surgery preoperative anxiety showed that music significantly reduced the stated anxiety in patients and no relation was found between the socio-demographic features, gender and type of surgery^[17]. In a study by Merakou *et al* which evaluated 200 patients who underwent cataract surgery, it was demonstrated that meditation music had an effect on preoperative stress and anxiety and reduced their systolic blood pressure. They recommended that music could be used as an alternative method to stabilize blood pressure in patients undergoing cataract surgery^[18]. Studies revealed that there are some reasons for the effect of music on reducing the anxiety. Music up-regulates the activity in the mesolimbic dopaminergic, which are related to stress and pain^[19,20]. It also down-regulates the activity of the central nucleus of the amygdale, which reduces the levels of fear and worries and down-regulates the activity of hypothalamic and brainstem nuclei that is responsible for the generation of the endocrine and vegetative stress responses^[21,22]. Since music consumes cognitive resources, patients might have been more distracted from fearful and worrying thoughts^[23]. Many studies have shown that listening to pleasant music reduces cortisol levels, a hormone related to anxiety^[15,24,25].

In the current study, no significant difference was seen in pre-test and post-test results in ear plug group, which means that using ear plug during surgery was not effective in reducing anxiety in subjects. It seems that separation of patients from the environment and the surrounding events by ear plug not only has no effect in reducing anxiety, but also has an adverse effect. In a study by Gonano *et al* in Austria in 2010 on 50 patients who underwent orthopedic surgery, after using propofol, patients of intervention group used ear plugs. Similar to our study, they found that the ear plug has no independent sedative effect^[9]. In Puri *et al's* study which was performed on patients

undergoing surgery with regional anesthesia, it was demonstrated that both music and ear plugs were effective in reducing anxiety and their result about ear plug was in contrast with the present study^[26].

In this study, in music and control subjects who were related to parity I group, the mean scores were significantly different before and after the intervention, which may show higher anxiety in parity I group. Since all subjects were related to low income families, we couldn't assess the effect of socio-economic factors on the result of the test. In addition, in subjects under 30 years of age, the difference between pre- and post-test scores was significant. The difference was also significant in individuals with under diploma educational level. These findings may suggest that primipara and uneducated patients are more influenced by environmental factors compared to experienced and educated parturient. In a study by Yilmaz *et al*, there was a significant association between sociodemographic features of the patient, the presence of social support and the severity of preoperative anxiety, while no relation was found between the age of patients and the anxiety level^[27].

CONCLUSION

The result of the study revealed that only music has an effect on reducing anxiety in parity I group and those with under diploma level of education. Ear plugs showed no effect on reducing anxiety in pregnant women undergoing caesarian section using spinal anesthesia.

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Original Article

Evaluation of the Undergraduate Medical Education National Core Curriculum-2014: National Frame of Medical Education in Turkey

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ABSTRACT

Objectives: Transformation experienced in medical education and the unplanned increase in the number of medical faculties has necessitated addressing the issue of medical education on a national level. As a result, at the meeting of the Council of Medical Deans, it was decided that a new national framework for undergraduate medical education should be created. This study aims to evaluate the design/change process and outcomes of the National Core Curriculum-2014 (NCC-2014) for Undergraduate Medical Education.

Design: Qualitative study, content analysis

Setting: All medical faculties from Turkey

Subjects: An expert working group was formed with the participation of 20 academic members from 16 medical faculties and the NCC-2014 was developed by using evaluation meetings and workshops. The design/change process and outcomes of the NCC-2014 were evaluated by national consultations. Data obtained through national consultations were analyzed thematically by

three researchers independently.

Intervention: None

Outcomes and Results: Considering bio-psychosocial/cultural perspective, outcome-based and task-based education, the NCC-2014 was developed in the framework of four fundamental components: The Aim of Medical Education and The Frame of National Competencies" with the lists of the "Symptoms/Situations", "Core Diseases/Clinical Problems" and "Basic Medical Practices". The frame-program was evaluated positively by the stakeholders due to its "providing a perspective aimed at learning", "making contribution to the educational standardization of the faculties", "being functional" and "being a guiding light for practitioners".

Conclusion: Although the NCC-2014 is the first step towards the standardization of medical education, further planning aimed at internalizing the started change by all relevant institutions should be done.

KEY WORDS: core curriculum, outcome-based education, program evaluation, qualitative analysis, task-based education

INTRODUCTION

Recently, regarding the major problem areas faced in medical education, important transformations have been experienced. Among these, the following are those that come into prominence: (a) outcome-based, task-based and community-based educational approaches; (b) quality assurance and national/international standardization of medical education, (c) the humanities and social/cultural perspective in education, (d) selection/organization of huge

learning contents in a contextual/integrated way^[1-4]. Considering the literature, it is possible to handle these transformations in three perspectives:

1. As a more holistic approach, preferring learning outcomes instead of learning objectives^[5,6].
2. Designing a curriculum based on outcome-based and problem/task-based approaches^[7]. With the top-to-down approach, first of all, determining lists of problems/situations or tasks; after that, specifying related competencies, and finally

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selecting and organizing educational contents would be lined up.

3. Specifying educational content in a way that enables to cover related sciences like basic, clinical, social and humanities, and organizing these contents in a contextual/integrated way^[3,8].

In this context, medical education in Turkey has set off on an important quest both on the national level and at the level of medical faculties. The processes of the National Core Curriculum (NCC) and "accreditation in medical education" have come into prominence.

In our country, the first important step on a national level aimed at increasing the quality of medical education and ensuring national standardization was taken by the decision of the Medical/Health Sciences Education Council in 2001. As a consequence, the NCC-2002 was developed in 2002 and has been implemented and evaluated ever since^[9,10].

The existing NCC (NCC-2002), that is to say the medical education in our country, had the following problem areas:

- NCC-2002 was only made up of lists of "symptoms/clinical situations" and "core diseases/clinical problems". Apart from this, list of skills and attitudes were also given, yet these were not handy enough^[9]. The program did not have a national frame that should be present in a core curriculum to guide medical schools with main components like "educational outcomes", "educational content", "learning and assessment methods".
- In NCC-2002, the problem/situation list was limited to "symptoms" (e.g. nasal congestion) and "clinical situations" (e.g. hematuria). "Healthiness situations", "forensic or psychosocial situations" and "environmental and global situations" such as "growth and development", "healthy sex life", "violence", "abuse", "pollution", "climate change", "migration" and "terror", were not present. However today, such situations have been encountered more and more often by graduates in the health area, and therefore needed to be dealt with.
- According to the changes experienced in society's healthiness/disease profile and disease load, "core diseases/clinical problems" listed in NCC-2002 had to be revised and updated along with their required performances and learning levels.

Moreover, there have been two prominent challenges in the course of the past ten years. One of these challenges has been the growing impact imposed by the transformations experienced in medical education worldwide (outcome-based, task-based and community-based educational approaches; quality assurance and national/international standardization of medical education, the humanities and social/cultural perspective in education, selection/

organization of huge learning contents in a contextual/integrated way). The other challenge has been the rapid and insufficiently planned increase in the number of medical faculties in Turkey.

The placement of students to medical schools in Turkey is made by a two-step central placement test taken by high school graduates. There is no other requirement for the placement. All high school students take the tests, yet the placement to medical schools is made according to results of mathematics, geometry, physics and biology sections of these tests. Students are placed in one of the medical schools if they have a high score success in the tests (scoring within the uppermost group of 1 - 2%).

These challenges have necessitated the problem to be taken in hand again on a national level. Accordingly, at the meeting of the Medical Deans Council in December 2012, it was decided that a working group should be formed in order for a new national framework to be constructed. The working group was formed and as a result of one year-long work of the expert working group, the newly developed frame-program (NCC-2014) was accepted at the meeting of the General Assembly of the Higher Education Council dated June 19, 2014.

With the NCC-2014, it was aimed at offering to all partners that are related with medical education, a national frame in which the main bases and principles of undergraduate medical education are determined. Accordingly it aimed at reaching a certain standard in medical education on the national level in line with the contemporary educational principles and approaches. The two main purposes of this study were (1) to evaluate how functional the outcomes of the NCC-2014 were and (2) to analyze the design/change process with regard to its framework and quality of change planning/management process.

SUBJECTS AND METHODS

The process started with the decision made at the meeting of the Council of Medical Deans. After this decision, firstly, the medical deans were informed, and they were asked to be the members of the work group to be formed or to assign a representative each. As a result, an expert working group was formed with the participation of 20 academic members from 14 different departments. The group started to work in April 2013, and the process was completed in March 2014. In this process, in which two evaluation meetings and six workshops were held, nine presentations were made, and 31 group work sessions were conducted. At the end, the "Undergraduate Medical Education NCC-2014" was developed through the following steps.

Step 1-Evaluation meetings: In this step, two assessment meetings lasting one day each were

conducted. In these meetings, the NCC-2002 was reviewed. Decisions about the aims, approaches, principles and methods regarding the NCC-2014 were made. The following three approaches were adopted concerning the National CEP-2014: (1) Bio-psycho-socio-cultural perspective in all the processes of health care and education, (2) learning outcome-based approach, and (3) problem- and task-based approach. In this context, four main components of the undergraduate medical education were defined as "The Aim of the Undergraduate Medical Education and the Frame of National Competencies", "The List of Symptoms/Situations", "The List of the Core Diseases/Clinical Problems", and "The List of the Basic Medical Practices".

Step 2–Developing the first draft: In the direction of the approaches that were defined in the first step, the first draft of the NCC–2014 came into the light by four workshops, each lasting 2 - 3 days. During the workshops, the groups worked on the NCC-2002 and reviewed other related documents like national reports about health/disease load and core curriculum samples worldwide. As a result, three lists were formed: "The List of Symptoms/Situations", "The List of the Core Diseases/Clinical Problems" and "The List of the Basic Medical Practices". The learning levels of each item in the last two lists were defined.

During the workshops, two different approaches emerged for "the Frame of National Competencies". While some of the group members preferred to define the competencies list at a national level, others preferred just to construct a national frame for it and to leave the further determination of competencies to medical faculties. As a result, the group's decision was to handle this issue as a second section of NCC-2014, and that a separate group be formed and study it.

Step 3–Receiving partners' opinions about the program: The first draft of the NCC–2014 was sent to the partners to take their opinions as a national consultation. The partners with whom the draft was shared were all the medical faculties and other relevant institutions and organizations like medical education associations, specialist associations concerning primary health care, the Turkish Medical Association and the Ministry of Health. The consultation reports were received from 37 different institutions and organizations. Among these, 28 of the reports received were from medical faculties, and the rest were from various medical education-oriented associations, including medical students' associations. In the present study, the design/change process and outcomes of the NCC-2014 were evaluated by the thematic analysis of these consultation reports. In the thematic analysis, three researchers (MAG, EG and AS) independently

analyzed the consultation reports to identify common themes and categorizations. Upon the independent initial analyses through iterative processing, the researchers arrived at a consensus regarding common themes and categories. Themes and categories that emerged from this qualitative analysis are presented in the results.

Step 4–Putting the program into its final version: In the last step, two more workshops were conducted with the working group. All the consultation reports were reviewed, suggestions concerning the three lists (Symptoms/Situations, Core Diseases/Clinical Problems and Basic Medical Practices) were discussed and those deemed appropriate after the evaluation carried out were included in the program. Thus, the NCC-2014 took its final version. The constructed program was published into a handbook for all the partners related with medical education, and was implemented by the decision of the Council of Higher Education.

RESULTS

Outcomes of National Core Curriculum–2014: Problem and task lists

In the NCC-2014 in which problem-based and task-based approaches were adopted, the participants worked on the list of problems and tasks, which constitute three of the four main components of the program. The list of problems comprised the "symptoms and situations", while the list of tasks was composed of "core diseases and clinical problems" and "basic medical practices".

The list of symptoms/situations: The list of symptoms or situations is defined as "the situations of the first encounter which a doctor faces in a clinical setting or in other environments (school, workplace etc.), and which he/she has to manage". In accordance with the bio-psycho-socio-cultural perspective, symptoms and situations were collected under these subheadings: (1) "Symptoms" such as nasal congestion and "clinical situations" such as hematuria, (2) "forensic or psychosocial situations" such as violence, abuse, (3) "healthiness situations" such as growth and development, healthy sex life, and (4) "environmental and global situations" such as pollution, climate change, migration and terror (Table 1).

The list of the core diseases and clinical problems: Core diseases or clinical problems were defined as "the diseases such as appendicitis, which a doctor diagnoses or pre-diagnoses, or the clinical problems such as allergic reaction, which he/she identifies". At this stage, the following four criteria which include a disease or clinical problem in the "core" list were

Table 1: The National Core Curriculum–2014: The list of symptoms and situations

Subheadings	Number (%)	Examples of symptoms and situations
A. Symptoms and clinical situations	124 (71.3)	Anemia Anxiety Chest pain Sore throat
B. Forensic and/or psychosocial situations	18 (10.3)	Abuse Alcohol/substance use and addiction Death
C. Healthiness situations	19 (10.9)	Elderly health immunization School health Worker health
D. Environmental (physical, socio- cultural) and global situations	13 (7.5)	Climate change Immigration Inequalities in health Natural disasters (earthquakes, floods), poverty, starvation Urbanization
Total	174 (100)	

defined: (1) those which are encountered frequently in primary care settings, (2) those that are of vital importance and that require immediate intervention, although they are not encountered frequently, (3) those which have serious consequences/effects on individual, community and/or global health and (4) those which are to meet one of the first three criteria in the near future. After the criteria for the core list were defined, as a second step, 345 diseases/clinical problems were listed. Finally, the learning level for each disease/clinical problem was defined. These learning levels indicate, at the same time, the performance levels of disease/clinical problems for

the medical faculty graduate who is to provide health care at the primary setting. As can be seen in Table 2, the number of diseases/clinical problems defined at the “initial diagnosis” level within 345 core diseases/clinical problems was 163 (47.2%), this number fell down to 71 (20.6%) for “diagnosis” and to 41 (13.6%) for “diagnosis and treatment”.

After two lists were determined, the symptoms and situations were matched with relevant core diseases/clinical problems (Table 3). The matching was carried out by considering the cardinal symptoms of diseases/clinical problems. In this way, it was aimed to provide guidance to the parties, especially in defining

Table 2: The National Core Curriculum–2014: Core diseases and clinical problems

Core diseases/clinical problems		Examples to core diseases and clinical problems	
Learning level	Number (%)	Disease / clinical problem	Learning level
E: Emergency intervention	95 (27.5)	Pulmonary oedema	E
		Allergic reaction	D-E
		Acute kidney failure	D-E-C
		Depression	DT-E-C-F
InD: Initial diagnosis	163 (47.2)	Secondary hypertension	InD-F
		AIDS and HIV	InD-C
		Bronchiectasis	InD-C-F
D: Diagnosis	71 (20.6)	Facial paralysis	D
		Pneumothorax	D-E
		Dermatitis	D-F
		Neural tube defects	D-C
DT: Diagnosis and treatment	47 (13.6)	Tension type headache	DT
		Urticaria and angioedema	DT-E
		Iron deficiency anemia	DT-C
		Chronic obstructive lung disease	DT-E-C-F
C: Control	114 (33)	Rabies	InD-C
		Tetanus	D-E-C
		Allergic rhinitis	DT-C
		Eating disorders	InD-C-F
F: Follow-up	36 (10.4)	Heat stroke	D-E-F
		Side effects of medication	DT-E-C-F

Table 3: Examples of matching symptoms/situations with core diseases/clinical problems

Symptom/situation	Core diseases/ clinical problems	Learning level	Organ system	
Anemia	Malnutrition	DT-C-F	Multisystem	
	Megaloblastic anemia	DT-C-F	Hematopoietic	
	Iron deficiency anemia	DT-C	Hematopoietic	
	Lower gastrointestinal bleeding	D-E	Gastro-intestinal	
	Upper gastrointestinal bleeding	D-E	Gastro-intestinal	
	Hemoglobinopathies	InD-C	Hematopoietic	
	Leucaemia	InD	Hematopoietic	
	Aplastic anemia	InD	Hematopoietic	
	Blood/blood products transfusion complications	InD	Cardiovascular	
	Hemolytic anemia	InD	Hematopoietic	
	Hemolytic uremic syndrome	InD	Multisystem	
	Sore throat	Diphtheria	DT-C	Multisystem
		Upper respiratory tract infections	DT-C	Respiratory
		Head and neck cancers	InD-C	Multisystem

E: Emergency intervention; InD: Initial diagnosis; D: Diagnosis; DT: Diagnosis and treatment; C: Control; F: Follow-up

the content of education and planning the learning activities.

The list of basic medical practices: The basic medical practices, which constitute another main component of the NCC-2014, were grouped under six sub-headings and a learning level for each practice was defined. As is seen in Table 4, of all the 136 basic medical practices, 3 consisted of "medical history taking", 20 consisted of "general and problem-oriented physical examination", 9 consisted of "record-keeping, reporting and notification", 21 consisted of "laboratory tests and other relevant procedures", 68 consisted of "invasive and non-invasive applications" and 15 consisted of "preventive medicine and community medicine

applications". When the learning levels specified for each of these practices were taken into account, it was seen that 37.5% (51) of them were specified at the fourth level, 51.5% (70) at the third, 9.6% (13) at the second, and 1.4% (2) at the first levels.

The main components of National Core Curriculum-2014

Apart from the lists explained above, specifications on four main components that a core curriculum should possess have been included in NCC-2014. With the implementation of these components, a national core has been formed for medical schools to get guidance from while developing their own curricula. The four main components were the following:

Table 4: The National Core Curriculum-2014: basic medical practices

Basic medical practices Subheadings	Number (%)	Examples to basic medical practices Practices	Learning level*
A. Medical history taking	3 (2.2)	General, problem-focused history taking	4
		Assessment of mental status	4
		Psychiatric history taking	3
B. General, problem-focused physical examination	20 (14.7)	Examination of breast and axilla	4
		Musculoskeletal examination	3
		Informed consent	4
C. Record-keeping, reporting, notification	9 (6.6)	Prepare patient's file	4
		Examine occult blood on gaita	4
D. Laboratory tests and other relevant procedures	21 (15.5)	Read and assess direct radiographs	3
		Prepare and apply atele	4
E. Invasive and non-invasive applications	68 (50)	Pregnancy follow-up	3
		Normal, spontaneous delivery	2
		Perform lumbar puncture	1
		Immunization	4
		Workplace and retail inspection	3
F. Preventive, community-oriented medicine	15 (11)		
Total	136		

* (1) knowing how the application is performed, and explaining its outcomes to the patient; (2) performing the application in guidance; (3) performing the application in situations/cases which are not complicated, and (4) performing the application including complicated situations/cases.

- **National framework for educational outcomes:** In this section, a frame to constitute guidance to medical schools while they identify their educational outcomes was formed. This frame encompassed the following three main competency areas: (1) the technical and procedural dimension of medicine and the management dimension of health care processes, (2) medical knowledge basis, decision making and critical thinking, scientific approach and research, and (3) competencies on professionalism^[11].
- **Educational content:** The educational content was formed in NCC-2014 within the frame of three main scopes as to be in parallel with the educational outcomes: (1) basic medical practices, (2) basic, clinical and socio-behavioral knowledge that form the basis of medical practice, and (3) professionalism.
- **Learning and assessment methods:** In this section, presumably the most appropriate learning and assessment methods for each of the three main educational outcomes and contents have been listed separately (Table 5). Medical schools were provided with a wide spectrum of multiple learning and assessment methods that they can use

in this respect, such as interactive lecturing in large groups, problem based learning in small groups, learning and assessment in simulated settings, on the job learning and assessment, society-based learning and assessment, project-based and portfolio-based learning and assessment^[12-23].

- **Curriculum development process:** Within the frame of educational approach based on educational outcomes, processes and steps that medical schools may follow while developing their own curricula were defined. With the top-down approach, different program planning templates were formed, through which medical schools can define basic, clinical and socio-behavioral learning contents with proper learning and assessment methods setting off from “educational outcomes”, “symptoms/situations” and “core diseases/clinical problems”.

Results of thematic analysis consultation reports

The consultation reports received from the partners were analyzed and collected under four themes. The first two themes were related with the opinions concerning “main components of the program” (symptoms/situations, core diseases/clinical problems,

Table 5: Learning and assessment methods more properly used for three main educational outcomes and contents

Educational Outcomes/Contents	Learning/teaching methods	Assessment methods/tools
A. Basic medical practices	<ul style="list-style-type: none"> • Learning in simulated settings, multi-disciplinary skills laboratory, clinical skills laboratory. • On the job learning, bedside teaching, ambulatory care teaching. • Learning in primary care unites and community setting (community health centers, schools, workplaces, factories, patients' homes etc.) • Structured case discussion, multidisciplinary case discussion 	<ul style="list-style-type: none"> • Assessment in simulated setting (simulated/standardized patients examinations, objective structured clinical examinations-OSCE etc.) • Assessment in skills laboratory (checklists, global ratings) • Assessment in primary care unites and community setting • Work-based assessment (mini-clinical evaluation exercises-MiniCEX, direct observation of procedural skills-DOPS, case-based discussion-CbD) • Student logbook, modified student logbook
B. Basic, clinical, socio-behavioral knowledge; decision making/evaluation and critical thinking; scientific approach/research	<ul style="list-style-type: none"> • Interactive lecturing • Problem oriented interactive learning in large and small groups (problem-based learning-PBL, team-based learning-TBL, case-based learning, case-based collaborative learning, clinical tutorial) • Multidisciplinary learning session (panel, case discussion etc.) • Project-based learning • Independent self-study, peer-assisted learning • E-learning 	<ul style="list-style-type: none"> • Written exams, essays, case assessment (multiple-choice questions, extended matching items, modified-essay questions, constructed-response questions, key-feature approach questions etc.) • Structured oral exam • Performance assessment in small group interactive tutorial sessions (PBL session, clinical tutorial etc.) • Self-assessment, peer-assessment • Report writing, holistic/analytic rubrics • Projects, portfolios
C. Professionalism	<ul style="list-style-type: none"> • Multidisciplinary learning sessions (panel, forum, case discussion etc.) • On the job learning • Critical incidents • Reflection sessions • Narrative writing • Role modeling, supervising, mentoring • Portfolios, reflective portfolios 	<ul style="list-style-type: none"> • Structured oral exam • Critical incident report, group reflection • Work-based assessment (Professionalism mini-evaluation exercise-P MEX, mini-peer assessment tool-MiniPAT, 3600 assessment) • Project-based assessment • Portfolios, reflective portfolios

basic medical practices) and “the content and format of the program handbook”. A large number of definite proposals concerning the main components of the NCC-2014 were reviewed one by one by the working group, and some of the suggestions were reflected on the lists to put them into their final version. Proposals concerning the content and the format of the program handbook were also discussed by the working group, and most of those proposals were reflected in the final version.

The remaining two themes were related with the opinions concerning the “reconstructing process of the NCC-2014 and the framework of the program” and “different approaches, frameworks and understandings as to the NCC concept”. The thematic analysis of these two themes was carried out by the three researchers of this study and the details were presented in Table 6 together with sample statements.

DISCUSSION

By way of the NCC-2014, a national framework concerning undergraduate medical education has been formed in our country. This framework is going to form a basis for all the medical educational processes/applications, including the quality improvement and national standardization/accreditation process. Thus, this framework is certainly very important for the medical faculties that are going to plan, develop and evaluate their own educational programs. With NCC-2014, a national core curriculum was formed for undergraduate medical education at medical schools. Medical schools are expected to plan and develop their own programs for pre-clinic and clinic educational phases and years according to this national framework. For this reason, no specification was made with NCC-2014 for pre-clinic and clinic educational phases and bases of years. It was deemed more appropriate that detailed specifications in this respect be made by medical schools themselves.

Furthermore, no specific process was defined in NCC-2014 on how to proceed to clinic education period from the pre-clinic one or onto the graduation process. This issue was left to individual medical schools. Also in our country, graduates of medical schools are able to practice medicine at the primary care centers as general practitioners, before which no national qualification testing is required. However, graduates who want to carry on their education in an area of specialization are placed to residency education by way of a central placement test. Accordingly, after the NCC-2014 was developed, a study committee was formed to re-define the content and the format of questions to be present in this national exam held for the placement of graduates to specialty fields of education. This committee formed a system in order to determine the number, areas and

the formats of questions to be asked in the examination for specialty in medicine according to the national framework defined by NCC-2014.

In the bio-psycho-socio-cultural context of the NCC-2014, the list of symptoms and situations was not formed by just the remaining items limited to symptoms and clinical situations. Besides symptoms and clinical situations, 50 situations were listed under the subtitles ‘forensic and/or psychosocial situations’, ‘healthiness situations’ and ‘environmental and global situations’. By doing this, it was aimed at forming the foundation in order to handle the psychosocial, environmental and global situations in education programs in a much more comprehensive and effective way. These situations can be exemplified as violence, abuse/neglect, school health, health care for risky/vulnerable groups, immigration, terror, *etc.*

Within the frame of problem-based and task-based education approach in the NCC-2014, the lists of symptoms/situations, core diseases/clinical problems and basic medical practices were determined together with the learning levels. Those lists are very useful to be able to cope with the huge educational content of medicine (selection and integrated/contextual organization of basic, clinical and behavioral/sociocultural contents). For instance, when the lists generated are examined within the context of coping with the intensive content of medical education, it is a positive result that almost half of the core diseases and clinical problems are being coded as “initial diagnosis”, and that those which are coded as “diagnosis”, “emergency medical intervention” and “diagnosis and treatment” remains between the range of 14% - 28%. So, this range presents an opportunity to medical faculties to design more focused programs, giving the priority to the diseases/clinical problems coded with “diagnosis”, “emergency medical intervention” and “diagnosis and treatment”.

When the opinions that came back from the partners as consultation reports concerning the NCC-2014 (Table 6), it was observed that, in general, the national frame that was developed was responded to positively. From among the positive suggestions, the most comprehensive ones can be briefed as ‘widening the active participation to all partners’, ‘developing the NCC on the basis of four main components, not just symptoms and diseases’, ‘being functional’, ‘presenting a learning perspective’, ‘providing convenience and guidance’, and ‘contributing to the standardization of education in medical faculties’. However, when the partners’ opinions were examined further (second title of Table 6), an important problem was observed. This problem was related with the conflict between outcome-based and task-based approaches adopted in the NCC and the existing education perspectives and

Table 6: Opinions of the stakeholders about the National Core Curriculum-2014

Themes	Categories	Sample statements / phrases
Reconstructing process and the framework of the program	Encouraging and widening active participation	<p>"We take kindly to asking opinions from the faculties and relevant institutions"</p> <p>"Although it is a work that has been prepared by a large participation, absence of some clinical branches is perceived"</p> <p>"Representatives from the General Practice Association and other relevant associations, the Turkish Medical Association being in the first place, should be included in the working group"</p>
	The national framework drawn by the program and the main components of the program	<p>"It has been a positive approach that the National Core Curriculum was prepared on the basis of four main components, not just a list of diseases and symptoms"</p> <p>"It is good that the subtitle 'healthiness situations' was included in the list of the symptoms/situations, with regard to emphasizing that the given situations should definitely take place in the curriculum"</p> <p>"The matching list is something quite befitting. It is going to provide a learning oriented perspective"</p> <p>"It was thought that the matching list was a table that is extremely functional and a list which perhaps make contribution to the education standardization"</p> <p>"Having the symptoms/situations and core disease/clinical problems being matched is going to be a very important guide to the implementer"</p>
Different (existing) approaches/frameworks with different understandings and misunderstanding	Educational approach and understanding based on instructional objectives and content of basic and clinical disciplines	<p>"The core curriculum can be defined as to what the minimum knowledge, skill and attitude should be in the content of the curriculum"</p> <p>"In the Basic Medical Practice list, 'communication skills', 'intellectual skills', 'skills to access information' should take place"</p> <p>"The concepts of ethics and professional values failed to satisfy"</p> <p>"The topics which should take place with the subtitle 'Ethical applications' under the title 'The List of Basic Medical Practices': Normative systems, Medical ethics and the relevant concepts, Ethical principles and doctrines..."</p> <p>"It is suggested that the titles 'Care for cancer patients' and 'Basic principles for radiotherapy' should be included in the program"</p>
	Basic sciences education	<p>"There is no knowledge concerning the content of basic sciences"</p> <p>"The care shown to clinical sciences in the National Core Curriculum was not shown to basic sciences"</p>
	Expectations that exceed the National Core Curriculum	<p>"It should be shown which competence should be taught by which department or departments"</p> <p>"After the number of annual course hours is set, the departments that will contribute to the students in the first three years and the course subjects of them, together with their content rates, should be specified"</p>

experiences of the medical faculties (content-based education and learning objectives perspective). This issue points out the need that the new planning has to be carried out at national and institutional levels in order to share the educational approaches and framework presented in the NCC-2014 and to have these internalized by the relevant institutions. If the planning is not carried out this way, inconsistencies between the framework presented by the NCC-2014 and the existing education perspectives of the medical faculties are going to arise. As a consequence, this will bring about the weakening of the change which has started.

The progress which was already made and is going to be made within the framework generated by the NCC-2014 should be seen as a progress which necessitates radical changes in medical education at national and institutional levels. Such change processes are complex ones that contain within themselves the problems, ambiguities and conflicts; opportunities, risks and threats. It is the process of manifesting a vision for the future, forming a framework for change, progressing within this framework and rendering this change sustainable. In other words, this process means forming

a well-designed plan and framework for change and reaching agreement in this framework. It also means forming a confirmative and supportive environment/ climate for change by effective communication and widened active participation. Since it is a complex process experienced with its rationalistic/intellectual, emotional and sociocultural dimensions, managing change means managing complexities, differences, uncertainties and conflicts^[24,25].

Eight errors have been listed by Kotter (2007), which are encountered frequently and which cause the failure of change effort. Among these, insufficiency in establishing sense of urgency, lack of having the change shared adequately by the partners, lack of systematic and efficient planning, lack of consolidation of change and lack of transformation of change into organizational culture can be mentioned first and foremost. When reviewed from this point of view, initiating, implementing and sustaining change are closely related to create an environment/climate of change, which is confirmative, supportive but challenging at the same time. In this context, in order to visualize/frame the change process, a diagram is constructed and presented in Figure 1. According to

this, during the change process, every effort is aimed at attracting the partners to the middle zone (zone of change/development), because both the “destructive zone” and the “comfort zone” are areas which are closed to change/development, even when different processes are experienced. Regarding the frame drawn in Figure 1, the reflection on the change process experienced with the NCC-2014 brings out three main points of consideration. It is possible to summarize these points as follows:

Meaningfulness, functionality, instrumentality

The framework drawn by the NCC-2014 has been found meaningful and functional/instrumental by the partners. It has also been stated that the program will guide the institutions, it will present a point of view aimed at learning and it will contribute to the standardization of the medical education in our

country. It can be said that this situation is one of the most important points that affect the process of change in a positive way, and that supports the change.

Planning the change, sharing the need for and the framework of change, empowering partners with active participation

The experiences during the process have shown that planning the change process effectively is one of the first and most important steps. However, the process experienced has indicated a relative weakness. This weakness points to the need to designate a clearer course of action that should aim at sharing with the stakeholders of the plan who designed the need for change and its framework, and outcomes that might come into being during the process of change. Another point which was relatively weak in the planning of the process of change was about forming the working

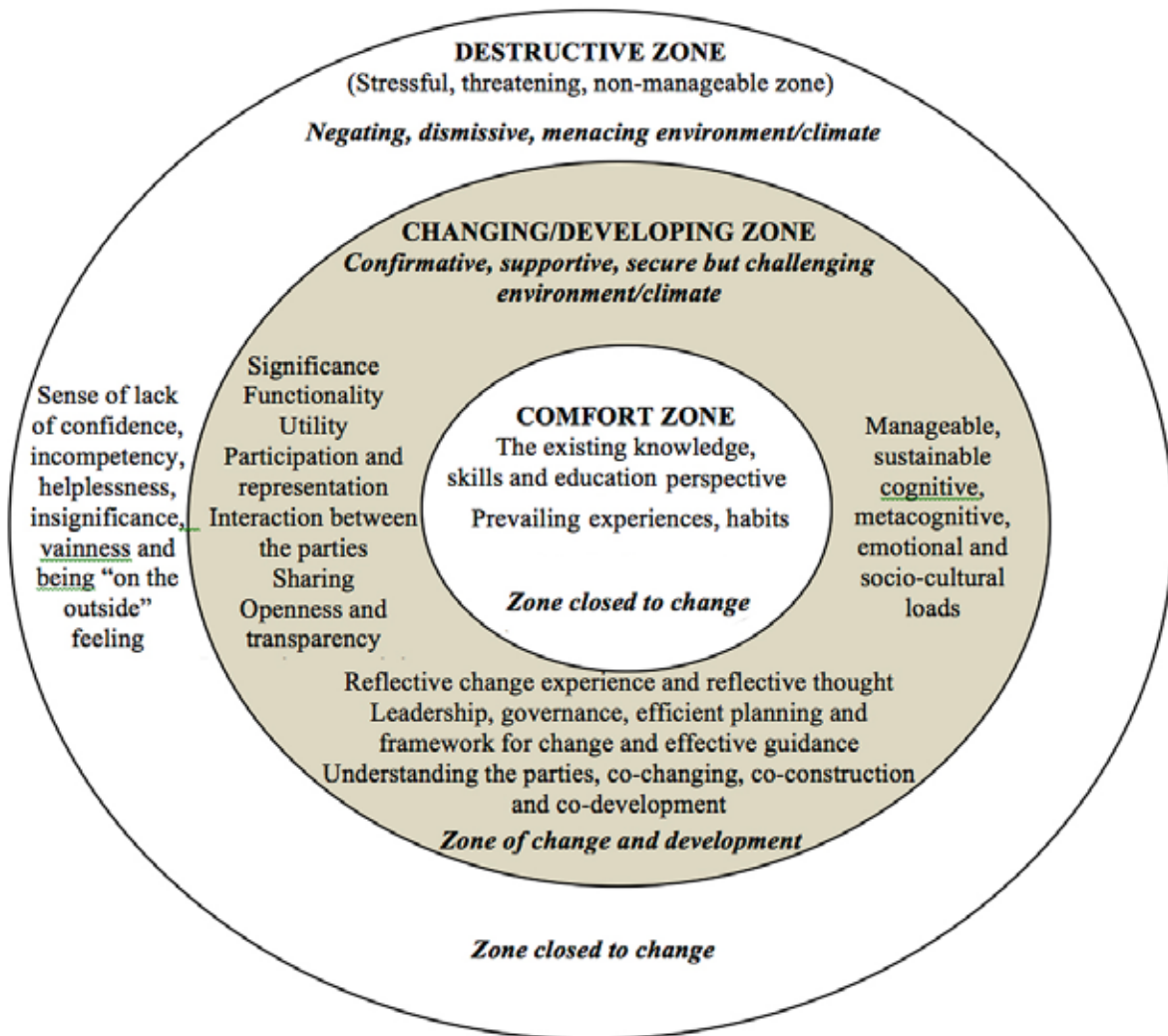


Fig 1: Three zone of change and development with different environments/climates of change.

group/keeping the representation within the group wide enough.

Overcoming obstacles and habits that are in conflict with the framework the change presents, and that lie ahead

The NCC-2014 was prepared with an educational approach which was outcome-based instead of learning objectives, with a problem-based and task-based approach instead of a content-based one. As Newble et al stated, by the top-down approach, outcome-focused core curriculum developed around problems and/or tasks and related learning contents are selected and integrated based on these. However, this situation caused conflicts with the existing experiences and habits of the parties. For example, according to some partners, the NCC was understood as 'the minimum knowledge, skill and attitude lists which have to be in the content of the curriculum'. So this was illustrated by the incoming suggestions from them on adding subject titles to the disciplines such as 'Medical ethics and the relevant concepts', 'the ethical doctrines and the principles of medical ethics', and 'the basic principles of radiotherapy'.

CONCLUSIONS

By way of the NCC-2014, a national framework well accepted by the partners was formed, and the first step was taken, aiming at standardizing and improving the quality of medical education at the national scale. However, when the framework presented with the NCC-2014 and the reflection of the change process experienced are taken into consideration, the need for further planning aimed at implementing and internalizing this process of change by all the relevant institutions and the need for providing the sustainability of change emerges clearly.

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Original Article

Impact of Ventilation Modes with Different Laparoscopic Access Routes on Blood Gases during Laparoscopic Urologic Surgeries: A Pilot Study

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ABSTRACT

Objectives: Our aim was to evaluate the effects of ventilation modes and different urologic laparoscopic approach techniques on blood gases.

Design: Retrospective view of prospective collected data

Setting: Clinical study was conducted at Afyonkarahisar University School of Medicine

Subjects: Patients undergoing laparoscopic urologic surgeries were enrolled. Groups were created as traditional (TV) and low tidal volume ventilation (LTVV) according to the used ventilation modes, and surgical access methods such as transperitoneal and retroperitoneal routes.

Intervention: Mechanical ventilation

Main outcome measures: Patients who underwent TV with transperitoneal approach were included in Group 1 (n = 21), TV with retroperitoneal approach constituted Group 2 (n = 29), LTVV with transperitoneal approach consisted Group 3 (n = 21), and LTVV with retroperitoneal

approach consisted Group 4 (n = 24). Statistical analyses were performed and significant p was $p \leq 0.05$.

Results: Ninety-six patients with mean age of 59.6 ± 11.3 were enrolled into our study. Minimum pCO_2 and maximum pH was determined in Group 3, maximum mean pO_2 was determined in Group 4, and pCO_2 was associated with ventilation type in the 1st and 3rd hour of operations ($p < 0.001$). The most common complication associated with CO_2 insufflation was subcutaneous emphysema and was classified as Clavien grade 1. There were 3 such patients each in Groups 1 and 4, 4 patients in Group 3, and 2 patients in Group 2. There was no need for additional interventions.

Conclusions: LTVV with transperitoneal approach can provide better arterial blood gas parameters during prolonged operations, and retroperitoneal approach may be useful for short operations.

KEYWORDS: laparoscopy, retroperitoneal space, surgical technique, ventilation

INTRODUCTION

Laparoscopic surgery has opened up a new era for minimally invasive surgery in urology^[1,2]. However, there are well-known benefits of laparoscopic surgery, carbon dioxide (CO_2) is mostly used during laparoscopic procedures worldwide and may cause to change respiratory measurements^[3]. These may also cause a change in blood pH parameters, notably during prolonged operation time, indirectly. Therefore, researches have been carried out regarding safer surgery methods during laparoscopic surgery. In order to evaluate better hemodynamic and surgical outcomes during laparoscopic procedures, there are some published studies on ventilation techniques

during laparoscopic surgeries^[4-7]. Protective ventilation usually includes low tidal volume ventilation (LTVV) in the range of 4 – 6 ml/kg of predicted body weight, and there are several reports on safety of LTVV during laparoscopic surgeries^[6,7]. The LTVV was developed for reduction of some disadvantages in traditional ventilation (TV)^[8].

On the other hand, transperitoneal^[9] and retroperitoneal^[10] approach techniques have been used for laparoscopic urologic procedures. Both of them have distinctive advantages as well as disadvantages. Thus, surgeons should prefer laparoscopic approaching methods in which they are experienced^[11].

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Both ventilation modes (LTVV and TV) and laparoscopic approaching techniques (transperitoneal and retroperitoneal) may affect CO₂ levels in blood as well as levels of free oxygen radicals^[12]. We would like to emphasize that there has not been any published data to determine which is the best combination of ventilation mode and laparoscopic surgical approach techniques.

In the present study, we evaluated levels of blood gases during laparoscopic surgeries in the light of changing laparoscopic approach techniques with changing ventilation modes. To the best of our knowledge, this pilot study is unique in the literature about which ventilation mode is more suitable for which laparoscopic approach.

MATERIALS AND METHODS

Study groups

This study included retrospective evaluation of our clinical prospective recorded data. Data was collected from files of patients, whose written informed consents were obtained for the study. Additionally, Institutional Review Board and ethical committee approved our study. All data were recorded to a Microsoft Office Excel spreadsheet, dating between August 2010 and November 2015. Exclusion criteria were lack of data, conversion to open surgery, comorbidity related with lung and breathing, American Society of Anaesthesiologist (ASA) score greater than 2, and patients with previous inguinal hernia repair or present inguinal hernia. The presence of pre-existing inguinal hernia or patency of the inguinal canal during transperitoneal approach may lead to scrotal, inguinal and prepubic emphysema. The accumulation of CO₂ may increase the hypercapnia level in these patients. A proper manual compression before trocar removal at the end of procedure will reduce further CO₂ absorption. There was no cut-off time period for surgical procedures in changing approaches. Totally, 95 patients were enrolled in the study and divided into groups according to the ventilation modes and laparoscopic approach techniques used. Patients who underwent TV with transperitoneal approach were included in Group 1 (n = 21), TV with retroperitoneal approach were included in Group 2 (n = 29), LTVV

with transperitoneal approach were included in Group 3 (n = 21), LTVV with retroperitoneal approach were included in Group 4 (n = 24).

All complications were noted according to Clavien-Dindo classifications^[13].

All patients underwent general anaesthesia. Monitoring with electrocardiogram, pulse oximetry and capnography were noted. Invasive blood pressure was measured during laparoscopic operations. Premedication began with intravenous injection of 0.1 mg/kg midazolam just before induction of anaesthesia. General anaesthesia was induced with propofol (1 - 2 mg/kg), fentanyl (1 - 2 mcg/kg), rocuronium (0.6 mg/kg) and maintained with desflurane, rocuronium and fentanyl. The peak and plat pressures of ventilation were monitored on ventilator.

Data collection

Arterial blood samples (from radial artery) were collected: after induction of anaesthesia, at the end of the 1st hour, and 3rd hour during operation. Additionally, the differences between 1st and 3rd hour parameters of CO₂ pressure (pCO₂), bicarbonate (HCO₃), pH, and mean oxygen pressure (pO₂) were worked out and recorded.

Laparoscopic urologic procedures

Laparoscopic procedures were performed either by transperitoneal or by retroperitoneal route. Patients were placed in lateral kidney position for renal surgeries and supine Trendelenburg for prostate surgeries. Access into operation area was provided by Hasson technique. Retroperitoneal space was created by retroperitoneal balloon dilators (Herloon, BBraun, Aesculap AG, Tuttlingen, Germany). After that, pneumoperitoneum/retroperitoneum was adjusted to 12 mmHg pressure even in transperitoneal or retroperitoneal approaches. All the surgical procedures done in the four groups are summarized in Table 1.

Statistical analyses

Statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS) for Windows 16.0 (SPSS Inc., Chicago, IL). Mann-

Table 1: Laparoscopic operation procedures in groups

Urologic laparoscopic procedures	Group 1 (n = 21)	Group 2 (n = 29)	Group 3 (n = 21)	Group 4 (n = 24)
Laparoscopic radical nephrectomy	7	9	4	3
Laparoscopic kidney cyst excision	2	3	5	7
Laparoscopic simple nephrectomy	5	7	3	4
Laparoscopic pyeloplasty	1	1	2	2
Laparoscopic radical prostatectomy	4	5	4	4
Laparoscopic partial nephrectomy	2	4	3	4

Table 2: Demographic, perioperative, and postoperative data in groups

Parameters	Group 1 (n = 21)	Group 2 (n = 29)	Group 3 (n = 21)	Group 4 (n = 24)	p-value
Age \pm SD (years)	56.1 \pm 10.5	63.1 \pm 13	59 \pm 11.5	59.2 \pm 8.9	0.1
BMI \pm SD (kg/m ²)	26.7 \pm 2.6	26.1 \pm 2.3	26.9 \pm 3.7	25.5 \pm 2.4	0.3
Smoking status (n (%))	5 (23.8%)	6 (20.7%)	3 (14.3%)	5 (20.8%)	0.8
Operation time \pm SD	224.8 \pm 30.9	260 \pm 57.7	224.5 \pm 64.4	245 \pm 71	0.09
Mean artery pressure \pm SD (mm/Hg)	73.4 \pm 6	73.1 \pm 6	76.8 \pm 7.9	75.2 \pm 6	0.1
Mean heart rate \pm SD	74.6 \pm 7.1	73.7 \pm 7.4	76.7 \pm 8.3	71.1 \pm 7.7	0.1
Hospital Stay \pm SD (day)	3 \pm 1.2	3 \pm 1	3 \pm 1.3	3 \pm 0.9	0.08

BMI: Body mass index, SD: Standard deviation

Whitney U-test was used to compare continuous variables. Analysis of variance (ANOVA) test was used to compare preoperative and postoperative variables. Pearson's correlation test was used to identify correlations between parameters. Statistical significant p-value was $p \leq 0.05$.

RESULTS

The mean age was 59.6 ± 11.3 years. There were 95 patients (66 male and 29 female) in the study. There were 21, 29, 21, and 24 patients in Group 1, 2, 3, and 4, respectively (Table 1). There were no significant differences in the demographic data as well as the operative time, artery blood pressure, and hospital stay among groups (Table 2). Mean follow-up was 10.71 ± 1.2 months.

The minimum pCO_2 was determined in Group 3 in the 1st and 3rd hour of operations ($p = 0.003$, $p < 0.001$ respectively). Additionally, optimal pH was obtained in Group 3, in 1st and 3rd hour of operations ($p < 0.001$, $p < 0.001$ respectively). Maximum mean pO_2 was determined in Group 4 ($p = 0.03$). Besides these, statistically significant higher maximum

blood oxygen level (spO_2) was obtained in Group 4 ($p < 0.001$). These were shown in Table 3.

Correlation tables were used for determining statistically significant relations in parameters (Table 4). Thus, the association of pCO_2 with ventilation type in the 1st and 3rd hour of operations was statistically significant ($p < 0.001$, $p < 0.001$ respectively). Additionally, delta pCO_2 ($[pCO_2$ at the 3rd hour of operation] – $[pCO_2$ at the 1st hour of operation]) was significantly associated with ventilation mode and access route ($p = 0.04$, $p = 0.002$ respectively). Moreover, delta pH ($[pH$ at the 3rd hour of operation] – $[pH$ at the 1st hour of operation]) was significantly associated with access route ($p = 0.009$).

The most recorded complication associated with CO_2 was subcutaneous emphysema and these were classified as Clavien grade 1. Subcutaneous emphysema was observed in 3 patients each in Groups 1 and 4, 4 patients in Group 3, and 2 patients in Group 2. These did not affect our clinical follow-up strategies or need additional interventions. There was no additional complication.

Table 3: Blood gas levels during laparoscopic surgeries

Parameters	Group 1 (n = 21)	Group 2 (n = 29)	Group 3 (n = 21)	Group 4 (n = 24)	p-value
$SpO_2 \pm$ SD	97.6 \pm 1.1	97.6 \pm 0.9	98.4 \pm 0.7	98.5 \pm 0.5	< 0.001*
p peak \pm SD	20.9 \pm 2.3	21.5 \pm 1.8	21.3 \pm 3	21.9 \pm 2.8	0.62
p plato \pm SD	16.8 \pm 2.1	16.8 \pm 2	17 \pm 2.9	16.5 \pm 2.2	0.94
$pCO_2 \pm$ SD	34.9 \pm 4.1	35.8 \pm 3.4	34.5 \pm 6.5	35.7 \pm 6.2	0.79
$pCO_2 \pm$ SD 1 st hour	48.9 \pm 9.1	46.5 \pm 6.7	41.2 \pm 6.7	43.4 \pm 5.2	0.003*
$pCO_2 \pm$ SD 3 rd hour	49.3 \pm 9.3	57.7 \pm 13.3	45.7 \pm 6	48 \pm 5.6	< 0.001*
Mean $pO_2 \pm$ SD	172.4 \pm 75.8	154.2 \pm 56.3	182.9 \pm 31.6	199.7 \pm 52.3	0.03*
pH \pm SD 1 st hour	7.2 \pm 0.1	7.2	7.3	7.3	< 0.001*
pH \pm SD 3 rd hour	7.2 \pm 0.1	7.2 \pm 0.1	7.3	7.3	< 0.001*
$HCO_3 \pm$ SD 1 st hour	22 \pm 2.4	21.2 \pm 2.3	21.8 \pm 2.1	21.1 \pm 3	0.54
$HCO_3 \pm$ SD 3 rd hour	20.3 \pm 2.4	20.8 \pm 4	21 \pm 2.5	20.6 \pm 3.2	0.90

SpO_2 : Blood oxygen level; p: pressure; pCO_2 : Carbon dioxide pressure; pO_2 : Oxygen pressure; HCO_3 : Bicarbonate; SD: Standard deviation
*Statistically significant p-value

Table 4: Correlation table of parameters that were recorded during laparoscopic urologic operations

Parameters	Ventilation mode	Access	Operation time in groups	pCO ₂ beginning	pCO ₂ 1 st hour	pCO ₂ 3 rd hour	Mean pO ₂	pH 1 st hour	pH 3 rd hour	Delta pCO ₂	Delta pH	
Ventilation mode	r	1	-0.047	-0.217	-0.027	-0.343	-0.346	0.225	0.442	0.363**	-0.122	-0.040
Access	p	0.6	0.03*	0.79	<0.001*	<0.001*	0.028*	<0.001*	<0.001*	0.04*	0.7	
Operation time in groups	r	1	0.082	0.101	0.002	0.276	-0.049	-0.008	-0.243	0.321	-0.267	
pCO ₂ beginning	p	0.4	0.3	0.9	0.007*	0.6	0.9	0.01*	0.002*	0.009*		
pCO ₂ 1 st hour	r	1	-0.187	0.025	0.109	-0.093	-0.038	-0.052	0.107	-0.019		
pCO ₂ 3 rd hour	p	0.07	0.8	0.2	0.3	0.7	0.6	0.3	0.8			
Mean pO ₂	r	1	0.529	0.313	-0.075	-0.353	-0.257	-0.072	0.070			
pH 1 st hour	p	<0.001*	0.002*	0.4	<0.001*	0.01*	0.4	0.5				
pH 3 rd hour	r	1	0.545	-0.186	-0.685	-0.494	-0.190	0.140				
Delta pCO ₂	p	<.001*	0.07	<0.001*	<0.001*	0.06	0.1					
Delta pH	r	1	-0.033	-0.385	-0.686	0.719	-0.383					
	p	0.7	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*					
	r	0.218	0.099	0.115	-0.110							
	p	0.03*	0.3	0.2	0.2							
	r	1	0.572	0.116	-0.373							
	p	<0.001*	0.2	<0.001*								
	r	1	-0.394	0.548**								
	p	<0.001*	<0.001*									
	r	1	-0.564									
	p	<0.001*										
	r	1										
	p											

pCO₂: Carbon dioxide pressure; pO₂: Oxygen pressure; Delta pH: (pH at the 3rd hour of operation) – (pH at the 1st hour of operation); Delta pCO₂: (pCO₂ at the 3rd hour of operation) – (pCO₂ at the 1st hour of operation)

*Statistically significant p-value

DISCUSSION

In recent years, laparoscopic urologic surgery has been widely used in daily clinical practise. Well known benefits^[14] and complications^[15] of laparoscopic surgery have been revealed. Additionally, laparoscopy can be performed for most of the urological surgery modalities in pioneer centres today^[16]. However, clinicians have made an effort to reduce complications. Increased CO₂ pressure in blood is one of the main problems we face during laparoscopic as well as robotic-assisted laparoscopic surgeries. In this case, some ventilation and medical interventions may come into question^[17]. Nevertheless, if urologists perform laparoscopy, they should know how to overcome those complications. In the present study, we investigated the effects of TV and LTVV on blood gases during different laparoscopic urologic procedures and access.

We found that pCO₂ significantly increased during prolonged retroperitoneal laparoscopic procedures with TV than transperitoneal ones. In a previous series, we already mentioned that ventilation mode was important for pCO₂ during urologic laparoscopic surgeries^[4]. In the present series, we found that the surgical access route could also play a role for pCO₂ during laparoscopic surgeries, in terms of statistical difference in gas parameters, which were changing according to laparoscopic approach technique.

There have been controversies in published studies for pCO₂ during transperitoneal and retroperitoneal laparoscopic approaches. Streich *et al* reported increased CO₂ absorption in retroperitoneal than transperitoneal CO₂ insufflation^[18]. This was similar with our results. In addition, Kadam *et al* concluded that pCO₂ and CO₂ absorption increased during laparoscopy, but they also reported that these did not depend on the route of surgery^[19]. On the other hand, Ng CS *et al* reported that retroperitoneal approach was not associated with increased absorption of CO₂^[20]. Furthermore, Wolf JS Jr *et al* found similar results with them and also reported significant absorption of CO₂ from peritoneum^[21]. These were in contrast with our results. According to our data analysis, we believe that transperitoneal route can be safer than retroperitoneal route when the surgical procedure would continue for more than 3 hours.

Absorption of CO₂ depends on some changing parameters. Notably, retroperitoneal space has more absorption capacity than transperitoneal one. Besides, some of the surgeons usually try to provide more space during retroperitoneal laparoscopic surgery. Specifically, when aspiration is used in retroperitoneal space, collapse in operation area comes into question. Therefore, surgeons try to expand surgical space by performing additional dissection in extraperitoneal space^[22]. In addition,

use of increased gas pressure can expand surgical space during operation. Thus, how much CO₂ would be absorbed from how much area in retroperitoneal space cannot be predicted. We think that changing results of absorption of CO₂ from retroperitoneal space may be based on those above^[18-21]. In contrast to this, the transperitoneal area is constant and absorption of CO₂ can be predicted^[23]. Therefore, we performed the present study to determine the exact factors for CO₂ absorption during laparoscopic urologic surgery in terms of different surgical route and ventilation modes. Furthermore, there is no doubt that increased absorption of CO₂ can cause complications^[24]. However, there was no gas embolism, and only subcutaneous emphysema was observed in groups without significant difference. Nevertheless, there was more subcutaneous emphysema in retroperitoneal access route. These may be related with uncounted absorption space of CO₂ in retroperitoneal laparoscopy.

There is no doubt that surgeons perform their technique for laparoscopic surgery. This can help to reduce complications^[25]. One of the present study's superiority is that all surgeries were performed by a single surgeon (M.A.) who has long term follow-up trained and same anaesthesiologist team. Our surgeon also performed all procedures with both access types and has similar experience for transperitoneal and retroperitoneal surgeries. Additionally, the same surgical techniques were performed in similar procedures. Therefore, we believe that we could avoid effect of surgeon and surgical technique on the outcome of the study. This was another feature of our study performing standard surgeries.

We strongly think that choosing laparoscopic approach technique can also help to reduce complications. Moreover, determining ventilation mode is important^[26]. According to our study, LTVV caused less pCO₂ than TV during all procedures. When LTVV was used in transperitoneal (Group 3), it looked like less pCO₂ occurred. Thus, significant optimal pH was recorded in Group 3 than other groups. Furthermore, the most increased O₂ pressure was observed in Group 4. This may be related with anaesthetist's technique for dealing with increased pCO₂ at the first time during operation. The correlation table showed significant association between delta pCO₂ and access route, ventilation mode. Besides these, there was significant correlation between delta pH and access route. These can be another reflection of importance of ventilation mode and access route in prolonged laparoscopic operations.

Kehlet *et al* reported that the anaesthetist plays an important role in reducing pain after operation^[27]. We agree with them and clinicians should conduct

anaesthetists to perform LTVV in prolonged laparoscopic surgeries. We think that collaboration with anaesthetist can make operation plausible during the course of operation, as well as during the follow-up of patient.

There are some limitations in our study. At first, the study was in retrospective pattern. Additionally, there were low numbers of patients in the groups and selection bias may come into question. Nonetheless, we focused on changing in parameters of blood gases during laparoscopic surgery.

Laparoscopic surgeons usually prefer laparoscopic approaching methods in which they are experienced. However, they should take into account the findings of the present study, such as the preference of transperitoneal route with LTVV in prolonged operations. However, long operation time in retroperitoneal laparoscopy may result in increasing blood CO₂ and HCO₃⁻. Clinical significance of the study shows that LTVV can be a practical option for long operation time in transperitoneal laparoscopic surgeries.

CONCLUSION

The combination of LTVV with transperitoneal approach seems safe in prolonged laparoscopic urological surgical modalities, specifically in operations which would take more than 3 hours. The LTVV with retroperitoneal approach may also be useful for short laparoscopic urologic procedures. Clinicians should also note the changes which occur in the blood gases during operation when prolonged laparoscopic urologic procedures are planned. More studies are needed for reducing complications during laparoscopic surgeries.

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Original Article

The Relationship between Stress and Academic Achievement of Medical Students in King Saud University: A Cross-Sectional Study

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ABSTRACT

Objectives: To investigate the relationship between stress and academic achievement of medical students. It also aimed to explore the relationship between stress and other factors, *i.e.* gender, marital status, residence, smoking status, year of study, and income.

Design: A cross-sectional study

Settings: College of Medicine at King Saud University, Riyadh, Saudi Arabia

Subjects: Medical students at King Saud University in Riyadh between January and July 2014

Intervention: None

Main outcomes measure(s): Demographic characteristics, academic achievement, and level of stress which was measured by using a valid and reliable Arabic version of a 14-item Perceived Stress Scale that was developed by

Sheldon Cohen (1983).

Results: There were 500 medical students selected as participants, and there was a 92% response rate (n = 460). The total prevalence of stress was 49.3%. Gender was found to be an independent significant risk factor for the outcome variable of stress, as females had a significantly higher stress level than males (odds ratio = 1.58, 95% CI = 1.05 – 2.39, p = 0.027). Students' GPA, marital status, residency, year of study, income and smoking status were not significantly associated with the stress level.

Conclusion: The major finding of high stress among medical students which points to the need for establishing counseling and preventive mental health services as an integral part of routine clinical services being provided to them

KEY WORDS: academic achievements, medical education, medical students, Saudi Arabia, stress

INTRODUCTION

Stress is defined as "a mentally or emotionally disruptive or upsetting condition occurring in response to adverse external influences and capable of affecting physical health, usually characterized by increased heart rate, a rise in blood pressure, muscular tension, irritability and depression"^[1]. Stress is very prevalent in modern life and is cause for concern in students undertaking medical education.

The overwhelming burden of information that students must learn at medical school leaves minimal opportunities for students to relax and recreate, which can leads to high levels of stress^[2]. Furthermore, numerous researches have also revealed that depressive symptoms and suicidal ideation have been observed

in medical students who experienced relatively high levels of stress^[2,3]. The number of reports regarding stress in medical training has gradually increased throughout the years, which has also shown that emotional distress in medical undergraduates occurred at a higher rate as compared to general population prevalence rates^[4]. Firth conducted research in three British medical schools and results revealed that about 30% of the students experienced stress^[4]. Other studies also supported the prevalence of stress in the majority of medical students in different countries^[5,6]. The research of Abdulghani *et al* validated the same phenomena at the College of Medicine, King Saud University at Riyadh, Saudi Arabia, wherein more than half of the students experienced a high level of stress^[7].

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A number of past studies have shown that medical students have been negatively affected by emotional distress as revealed by their reduced level of academic and medical performances as well as development and acquisition of disorders related to their stress^[8-10]. It has also been found that stress may reduce the level of concentration, impede decision-making, and hinder students to establish rapport with their clients. Ultimately, these outcomes may lead to the detriment of future clinical practice that is marked by dissatisfaction and inadequacy.

There are inconsistent results about the relationship between academic achievement and the level of stress. Some studies have found that stress is associated with lower academic and clinical performance. For instance, a study done in Pakistan showed that higher levels of stress are associated with poor academic performance^[11]. Also, a study done in Malaysia among fourth year undergraduate medical students found that academic achievement is positively associated with stress level, with the same results being found in other studies^[12-14]. However, a handful of studies have shown that there is no association between stress among medical students and academic achievement. For instance, a study done in Saudi Arabia found that academic achievement is not associated with stress level^[7]. Researches conducted in several Asian developing nations have validated the prevalence of stress among medical students and emphasized the potential and role of medical education as a stressor^[5,6]. Nevertheless, these studies were restricted since the time duration was for the first two years of medical school and was not able to establish the association between scholastic achievement and stress.

A systematic review of literature through the use of the internet has shown that there were few studies conducted in Saudi Arabia regarding the relationship between the scholastic performance of medical students and their level of stress. The study mentioned above that was undertaken by Abdulghani *et al* in 2011 reported a high prevalence of stress (63%), and no association between academic achievement and stress in medical students from King Saud University, Riyadh^[7]. Another study conducted by El-Gilany *et al* in 2008 on medical students at King Faisal University, Saudi Arabia, found an overall stress rate of 28.9%, but they did not study the association between academic achievement and stress^[15]. This difference in stress prevalence and the effect of stress on academic achievement, in addition to personal experience of stresses during medical school, require investigation.

The present research study was conducted in order to investigate the association between the scholastic performances of medical undergraduates at King Saud

University and their perception of stress. The aim was also to observe any possible association between stress and gender, marital status, year of study, income, residency, and smoking status.

SUBJECTS AND METHODS

Settings and participants

A cross-sectional study was conducted to explore the association between academic achievement and stress among medical students at King Saud University in Riyadh between January and July 2014.

Instrument

Many measures have been used to determine psychological distress and depressive symptomatology among medical students. Some examples are Beck's Depression Inventory and the General Health Questionnaire (GHQ), but there are many other instruments^[2,5]. In the current research project, the Perceived Stress Scale (PSS-14) was used, which is designed to assess the level to which participants rated their lives as being stressful during the previous month.

The PSS-14 survey questionnaire is a validated tool composed of 14 items with a scale ranging from 0 to 4. Responses are categorized as never, almost never, sometimes, fairly often and very often. The respondents should answer based on their experience of one month before the survey has been issued to them. Published studies have shown that the PSS-14 has sufficient reliability and validity as a survey tool, which also has been translated into multiple languages, including Arabic^[16,17]. The PSS-14 has an internal consistency of 0.85 and a test-retest reliability of 0.85^[18]. For these reasons, we decided to use PSS-14 in our research.

The utilized scale yielded a single score that indicated the level of stress as perceived by the respondent. A range of 56 being the highest score and 0 as the lowest by the scale presents a cut-off point of 28. A score higher than the cutoff point would mean that the respondent has perceived a relatively high level of stress being experienced, while a score lower than 28 pertained to a low level of stress as perceived by the candidate. This cut-off value was selected in accordance with similar studies from Egypt and Pakistan^[16,19].

Data collection

There are five academic years in medical college: first, second, third, fourth, and fifth years. A proportional sample was taken from each year. Then, we approached the students during their classes. The students were asked to complete a self-administered questionnaire consisting of two parts: demographic

and academic information, and perceived stress scale. Academic achievement was measured by asking students about their grade point average (GPA). This GPA score was achieved by multiplying the final grade in each year of the course by the credit hours for each course, and then dividing by the total number of credit hours for that student. The result was then converted to a widely used 5.0 scale^[20].

The data collection was done in January 2014, one month before the examination period, to neutralize the effect of the actual examination stress. The privacy of the students was assured and a copy of the written instructions and objectives of the study was given to the students. The participation was entirely voluntary. Approval for conducting the study was obtained from the research ethical committee of the College of Medicine, King Saud University.

Sample size calculation

Based on a previous study done among the medical students at King Saud University, the prevalence of stress was 63%^[7]. The total number of medical students at King Saud University in 2014 was 1490. Therefore, we calculated that the sample required for our survey, with an allowable error of 5%, 95% confidence limits, 1.5 design effect and 10% for non-responders, would be 500.

Statistical analysis

Descriptive statistics were used to detail the medical students' characteristics. The score of perceived stress was calculated and stressed/non-stressed students were identified using a cut-off value of 28. Chi-square was used to investigate the association between stress, academic achievement and other study variables. Fisher exact tests were used when the conditions of the Chi-square were not met. To quantify the association between stress and other study variables, the odds ratio with a 95% confidence interval (CI) was estimated. A logistic regression model was used to identify independent predictors for academic stress.

The statistical software package, IBM SPSS Statistics for Windows (Version 22.0) (IBM Corp., Armonk, NY, USA), was used to analyze the data. A statistical test with a p-value < 0.05 was considered significant.

RESULTS

Of the 500 questionnaires distributed, 460 completed questionnaires were received, which is a response rate of 92%. More than half (63.3%) of the respondents were male. The majority were single (96.7%) and living with their families (85.2%). Their mean (\pm standard deviation) age was 22.25 ± 1.67 years. About half (51%) of the medical students have an excellent GPA, while only 1% have a poor GPA.

Table 1: Characteristics of medical students (n = 460)

Variables	n ^a (%)
Gender	
Male	291 (63.3)
Female	169 (36.7)
Marital Status	
Single	445 (96.7)
Married	15 (3.3)
Study Year	
First Year	107 (23.3)
Second Year	89 (19.3)
Third Year	77 (16.7)
Fourth Year	83 (18)
Fifth Year	104 (22.6)
Residency	
With Family	392 (85.2)
University	34 (7.4)
Private	34 (7.4)
Income Level	
Enough	443 (96.5)
Not Enough	16 (3.5)
Smoking Status	
Yes	37 (8)
No	423 (92)
Age	
< 22 Years	338 (73.5)
> 22 Years	122 (26.5)
GPA ^b	
Poor	3 (0.7)
Good	48 (10.4)
Very Good	175 (38)
Excellent	234 (50.9)
Stressed	
Yes	227 (49.3)
No	233 (50.7)

^a: Number; ^b: Grade point average

The prevalence of stress at all levels was about 49.3% (Table 1).

Table 2 shows the association between stress and other variables used in the study. The proportion of female students who had stress was higher (57.4%) than their male counterparts (45%), and the result was statistically significant (p-value = 0.015). There was no association between the perceived stress in medical students and GPA, age, marital status, study year, residency, income level or smoking status. These results were not statistically significant.

Table 3 shows the multivariable logistic regression analysis used to predict the medical students' perceived stress by their different characteristics. After adjusting for GPA, gender, age, marital status, study year, residency, income level, and smoking status, the only characteristic that could predict perceived stress is gender. The stress among female students was 58% higher in comparison to male students [Adjusted odds ratio (AOR) = 1.58, Confidence interval CI = 1.05 – 2.39, p-value = 0.027].

Table 2: Association between stress and the study's variables

Variables	Stressed Cases n ^a (%)	Non-Stressed Cases n (%)	p-value
GPA ^b			0.522
≤ Good	29 (56.9)	22 (43.1)	
Very Good	85 (48.6)	90 (51.4)	
Excellent	113 (48.3)	121(51.7)	
Age			0.641
≤ 22 Years	169 (50)	169 (50)	
> 22 Years	58 (47.5)	64 (52.5)	
Gender			0.015
Male	131 (45)	160 (55)	
Female	97 (57.4)	72 (42.6)	
Marital Status			0.173
Single	217 (48.8)	228 (51.2)	
Married	10 (66.7)	5 (33.3)	
Study Year			0.417
First Year	61 (63.6)	46 (36.4)	
Second Year	42 (47.2)	47 (52.8)	
Third Year	37 (48.1)	40 (51.9)	
Fourth Year	36 (43.4)	47 (56.6)	
Fifth Year	51 (49)	53 (51)	
Residency			0.316
With Family	189 (48.2)	203 (51.8)	
University	17 (50)	17 (50)	
Private	21 (61.8)	13 (38.2)	
Income Level			0.580
Enough	218 (49.2)	225 (50.8)	
Not Enough	9 (56.3)	7 (43.8)	
Smoking Status			0.439
Yes	16 (43.2)	21 (56.8)	
No	211 (49.9)	212 (50.1)	

^a: Number; ^b: Grade point average

DISCUSSION

The current study evaluated the association between perceived stress and academic achievement among medical students at King Saud University in Riyadh, Saudi Arabia. The secondary objectives were to investigate the prevalence of perceived stress in relation to gender, marital status, year of study, income, residency, and smoking status. These objectives are important to both medical teachers and students, as a high prevalence of stress among medical students needs more attention, as it may result in disturbed behavior of students and decreased learning ability, and could eventually affect patient care during their future career.

The overall prevalence of perceived stress in the study was 49.3%, which is lower than the two studies done in Saudi Arabia at King Faisal University and King Saud University, where the prevalence of perceived stress was 53% and 63.7%, respectively^[7,21]. Also, it is lower than the Thai study, which found the prevalence to be around 61.4%^[6]. However, the prevalence of perceived stress among our students was higher

Table 3: Predicting medical students' stress after adjusting by different variables

Variables	Adjusted OR ^a (95% CI ^b)	p-value
GPA ^c		
Good	-	
Very Good	0.45 (0.21-0.96)	0.041
Excellent	0.61 (0.31-1.21)	0.164
Age		
≤ 22 Years	1.14 (0.53-2.48)	0.732
> 22 Years	-	
Gender		
Male	-	
Female	1.58 (1.05 – 2.39)	0.027
Marital Status		
Single	-	
Married	1.72 (0.57 - 5.85)	0.348
Study Year		
First Year	1.85 (0.73 - 4.66)	0.188
Second Year	1.19 (0.47 - 2.97)	0.706
Third Year	1.04 (0.42 - 2.52)	0.929
Fourth Year	0.84 (0.39 - 1.79)	0.665
Fifth Year	-	
Residency		
With Family	-	
University	1.28 (0.61 - 2.68)	0.504
Private	1.72 (0.81 - 3.77)	0.157
Income Level		
Enough	-	
Not Enough	0.85 (0.28 - 2.62)	0.781
Smoking Status		
Yes	-	
No	1.12 (0.55 - 2.34)	0.740

^a: Odds Ratio; ^b: Confidence interval; ^c: Grade point average

than the El-Gilany *et al* study, which was conducted on medical students at King Faisal University, Saudi Arabia, and had an overall stress rate of 28.9%^[15]. It is also higher than the Egyptian study at Al Mansoura University (43.7%), the Malaysian study (41.9%), and a British study (31.2%)^[4,5,15].

Different instruments have been utilized by these researches that measured stress, although the differences in the methodologies have restricted their comparability. The PSS - 14 has been selected because its reliability and validity as an instrument has been well-documented^[18,22]. Another critical factor that has been considered in the selection process of the instrument was that the other assessment tools only focused on academic stressors but did not include psychosocial issues and reactions. This also limited their applicability in other settings with broader scopes^[22].

In our study, we found that the level of stress was at the highest level for students in first year, then it started to decrease, although the result was statistically insignificant. Results of other studies

in North America suggest that mental health worsens after students join a medical school and remains poor throughout the course, especially in the transition from basic science teaching to clinical training^[23]. This is due to the overwhelming volume of knowledge and materials required in medical college compared to secondary school, but after some time, the students start to become accustomed to this new environment.

The prevalence of stress in the study was significantly higher among the female students (57.4%) compared to their male counterparts (45%), which is similar to studies conducted in Pakistan and Saudi Arabia^[7,16]. In our study, being a female student means that your stress is increased by 58% when compared to a male student. A plausible reason may be the conservative nature of society in Saudi Arabia, where women lack the freedom to participate in extra-curricular activities owing to the restrictions imposed on them by the society. Therefore, their private life may conflict with their professional life and this may cause stress. However, this issue was not addressed in our study and requires further investigation.

The findings indicated that there was no apparent relationship between scholastic achievement and the perception of the level of stress by medical students. These findings proved to be similar to other studies conducted in universities in Pakistan and Saudi Arabia^[7,16]. The results have proven to be contrary to the previous researches with regard to acute stress being a predictor of diminished academic performance^[24,25]. Furthermore, such contradictory findings may be due to the circumstance that chronic stress may have a more significant impact on academic performance during exams. Moreover, the students may have compensated for their scholastic performance by taking appropriate measures for preparation before taking their examinations, which most probably decreased their vulnerability to emotional distress. More importantly, coping mechanisms along with familial and social support had a significant role in reducing their stress levels, although this was not examined in our research study.

Limitations

Several limitations can be noted in the study, which are: 1) information bias; 2) the cross-sectional study design; and 3) validation of GPA records. Information bias cannot be avoided since the study utilized a self-administered survey questionnaire. In addition, associations lacked temporality due to the cross-sectional design of the study. Despite a favorable response rate, wherein a majority of the respondents

were able to answer the survey questionnaire, the non-respondents should be interviewed regarding their reasons for not participating in the activity.

Recommendations

The results of the study suggest that the prevalence rate of stress was higher in female students as compared to their male counterparts, which was statistically significant. Despite higher stress levels being experienced by freshmen as compared to other year levels, this was not statistically significant. Although not statistically significant, stress had a negative relationship with academic performance. In addition, the research did not find any relationships between stress and other demographic variables, such as marital status, residency, income, and smoking status.

CONCLUSION

The resulting high level of psychological stress found in medical students of King Saud University indicate the necessity to provide adequate guidance and counseling as well as preventive mental health programs as part of the routine clinical programs for medical undergraduates. Candidates for medical school should also be interviewed and assessed for psychiatric problems before their admission as medical students.

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Conflict of interest: The authors declare no conflict of interest.

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Original Article

Serum C-reactive Protein Levels in COPD Patients after Eight Week Comprehensive Pulmonary Rehabilitation Program

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ABSTRACT

Objectives: To evaluate the effects of pulmonary rehabilitation (PR) program on C-reactive protein (CRP) levels and to identify the relationship between the changes in CRP levels with the outcome measures of PR with/without frequent comorbidities

Design: The patients' data before and after PR were evaluated retrospectively

Setting: Ataturk Chest Diseases and Surgery Education and Research Hospital, Ankara, Turkey

Subjects: One hundred and four stable, ex-smoker, chronic obstructive pulmonary disease (COPD) patients completing PR were enrolled into the study. Thirty-eight patients (36.5%) had a co-morbid disease.

Intervention: Out-patient, multidisciplinary, eight-week, comprehensive PR was performed

Main outcome measure: Serum CRP levels

Results: CRP levels decreased from 0.99 ± 1.50 to 0.62 ± 0.90 mg/dL. CRP level changes after PR were not significantly different in patients with/without comorbidities. Medical Research Council (MRC), St George's Respiratory Questionnaire scales, incremental and endurance shuttle walk test (ISWT, ESWT) (all $p < 0.001$), body mass index ($p = 0.038$), FVC% ($p = 0.032$), FEV1% ($p = 0.005$) improved significantly in all patients. Baseline CRP levels only correlated with baseline ISWT ($p = 0.037$, $r = -0.205$), ESWT ($p = 0.041$, $r = -0.201$). Only improvements in FVC% and CRP level correlated significantly ($p = 0.008$).

Conclusions: This study showed that there was negative correlation between CRP and exercise capacity in COPD patients and also, decreased CRP levels were associated with improvements in FVC.

KEY WORDS: exercise, inflammation, lung disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by low grade, persistent, chronic inflammation and is associated with significant systemic involvements^[1,2]. It has been reported that inflammation was related to co-morbidities of COPD^[3,4]. C-reactive protein (CRP) is an acute-phase reactant synthesized predominantly by hepatocytes responding to tissue damage or inflammation. Several systemic inflammatory markers or cytokines including CRP, interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor (TNF)- α have been shown to be related to COPD risk, mortality, exacerbations, or decline in lung function^[5-9]. Furthermore, positive relationship was indicated between CRP, IL-6, exercise tolerance, and health status^[7,9].

Exercise training is the cornerstone of pulmonary rehabilitation (PR). It has been shown to provoke the secretion of pro- and anti-inflammatory cytokines^[10,11], in accordance to the intensity and duration^[12,13]. In healthy population and patients with heart failure, exercise has been known to reduce serum CRP levels^[14,15]. However, the effects of long term exercise on CRP levels in COPD patients has not been identified clearly. The primary aim of this study was to evaluate the effects of PR program on CRP levels. The secondary aim was to identify the relationship between the changes in CRP levels with the gains of PR with/without frequent comorbidities.

SUBJECTS AND METHODS

The data of 104 stable COPD patients, who had completed an outpatient, eight-week PR program

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were investigated retrospectively. Patients' approval had been taken before the data were recorded.

Study population

Patients with any acute or chronic infection, acute exacerbation, active smokers and treated with systemic corticosteroids were not included in the study. Patients were using long and short acting beta agonists, anticholinergics and inhaler corticosteroids according to Global initiative for chronic Obstructive Lung Disease (GOLD) criteria^[6]. The patients who had one of the co-morbid diseases (hypertension (HT) or diabetes mellitus (DM)) were included into the study. Echocardiography was performed before PR in all patients.

Measurements

Dyspnea sensation was assessed with MRC scale, quality of life with St George's Respiratory Questionnaire (SGRQ), exercise capacity with incremental and endurance shuttle walk test (ISWT, ESWT) before and after the PR program. Body composition was evaluated by using bioelectrical impedance method. Body mass index and fat free mass index (BMI, FFMI) were calculated. Serum CRP levels were measured at the initial evaluation before PR and in a week after the completion of PR program. Plasma CRP was measured by a commercially available blood analyzer (Arcitect C8000, Abbott, Illinois, USA.)

Pulmonary rehabilitation program

The PR consisted of a comprehensive, multidisciplinary, hospital-based, supervised outpatient program twice a week and an unsupervised home exercise program once a week. The program consisted of education (which included disease education, how to control exacerbations, medication advices, bronchial hygiene techniques, and breathing control techniques, energy conservation, relaxation, and dietary advices), exercise training, psychological support, and nutritional support. Educational courses were given by two pulmonologists, two physical therapists, a dietician, a respiratory nurse and a psychologist. The rehabilitation program was completely tailored to suit the needs of the individual. According to guideline recommendations, the exercise program was also tailored to the individual and a group of exercises was chosen for each patient according to their ability to tolerate exercise and their disease severity. The exercise training and the sessions included cycle ergometer and treadmill training (15 min each), strength training of both upper and lower extremities (5 - 10 min), and therapies for breathing and relaxation (15 - 20 minutes each) for a total of 70 - 90 min/day. Patients underwent both cycle ergometer

and treadmill training. Both workloads for cycling and walking speed for treadmill ergometer were calculated from ISWT results using formulations and Borg dyspnea scores (4 - 6) were also used for prescribing exercise. Patients were trained at 50% of the peak workload on cycle ergometer and 60 - 85% of VO_2 peak on treadmill. Intensity of exercise was increased according to the progress of individual patient. Physiotherapists provided close supervision and heart rate, blood pressure and oxygen saturation were monitored during the training sessions. Supplemental oxygen was administered to level oxygen saturation above 90%.

Statistical analysis

SPSS version 18.0 (SPSS, Inc., Chicago, USA) for Microsoft Windows (Microsoft Corporation, Redmond, Washington) was used for analysis. Data are expressed as mean \pm SD. The variables were analysed with Shapiro-Wilks test for normal distribution. The paired t-test was used for variables with normal distribution, and Wilcoxon Signed Rank test used for those variables without normal distribution. Mann-Whitney U test was used to compare variables across groups with abnormal distribution and unpaired t-test for normally distributed variables. For correlation analysis, Spearman correlation analysis was used. Statistical significance was set to a p-value < 0.05 .

RESULTS

Ninety-three of the patients were male (89.4%). The mean age was 62.9 ± 7.9 years. All patients had a history of smoking and all were ex-smokers, and had a mean forced expiratory volume during the first second (FEV1) of 39.4 ± 17.4 . Seven patients were in group A, 18 were in group B, 22 were in group C and 57 were in group D according to GOLD classification^[6]. Thirty-eight patients had a co-morbid disease (36.5%). Twenty-four of them had only HT (23.1%) and fourteen had only DM (13.4%). The mean value of FEV1 of patients with comorbidity was 39.14 ± 17.72 of predicted %, and 39.5 ± 17.3 patients without comorbidity, disease severity according to FEV1 was not significantly different. Baseline CRP levels of patients with and without comorbidity also were not significantly different (0.94 ± 1.53 and 1.02 ± 1.50 , respectively).

The values before and after PR are summarized in Table 1. In all patients, MRC scales ($p < 0.001$), SGRQ scales (total and all domains $p < 0.001$) significantly decreased. ISWT distance ($p < 0.001$) and ESWT ($p < 0.001$) time increased significantly. BMI ($p = 0.038$), forced vital capacity (FVC)% ($p = 0.032$), FEV1% ($p = 0.005$) improved significantly. Before PR, it was found that CRP levels were correlated with baseline ISWT

Table 1: The values before and after PR

Recorded parameters	Before PR mean±SD	After PR mean±SD	p-value
Age (years)		62.91 ± 7.87	
Cigarette (per year)		60.26 ± 33.7	
CRP (mg/dL)	0.99 ± 1.5	0.62 ± 0.9	0.101
BMI (kg/m ²)	25.02 ± 3.58	26.2 ± 5.35	0.038
FFMI (kg/m ²)	19.38 ± 2.33	19.35 ± 2.2	0.76
MRC	3.02 ± 0.74	2.05 ± 0.6	< 0.001
SGRQ-symptom	73.37 ± 14.5	40.68 ± 11.78	< 0.001
SGRQ-activity	72.63 ± 17.55	42.59 ± 10.67	< 0.001
SGRQ-impact	59.87 ± 18.94	23.52 ± 10.03	< 0.001
SGRQ-total	66.07 ± 15.59	32.12 ± 8.29	< 0.001
FEV1% predicted	39.37 ± 7.39	42.45 ± 18.74	0.005
FVC% predicted	58.2 ± 19.26	61 ± 18.14	0.032
ISWT (meter)	236.15 ± 116.65	289.9 ± 115.35	< 0.001
ESWT (min)	7.71 ± 6.62	14.88 ± 7.08	< 0.001

PR: Pulmonary rehabilitation; CRP: C-reactive protein; BMI: Body mass index; FFMI: Fat free mass index; SGRQ: St George's Respiratory Questionnaire; FEV1: Forced Expiratory Volume in one second; FVC: Forced vital capacity; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test

distance ($p = 0.037$, $r = -0.205$) and ESWT ($p = 0.041$, $r = -0.201$) time. Even though CRP levels decreased from 0.99 ± 1.50 to 0.62 ± 0.90 mg/dL after PR, it did not reach significance. After PR program, mean CRP levels in patients with comorbidity was 0.85 ± 1.38 mg/dl, whereas it was 0.49 ± 0.38 mg/dl in patients without comorbidity. Although there was a further reduction in CRP levels of the patients without comorbidity, it was not found to be statistically significant. The improvements in the other outcome measures were also not statistically different according to the presence of comorbidities (Table 2).

Table 2: CRP level of patients with one comorbidity and without any comorbidity

CRP levels	Patients with one comorbidity	Patients without any comorbidity	p-value
Before PR	0.94 ± 1.53	1.02 ± 1.5	0.976
After PR	0.85 ± 1.38	0.49 ± 0.38	0.395
Change in CRP	- 0.08 ± 1.91	- 0.53 ± 1.43	0.539

CRP: C-reactive protein; PR: Pulmonary rehabilitation

The change in CRP levels were compared with the changes in BMI, ISWT, ESWT, MRC, SGRQ all domains and total score, FEV1% and FVC% in all patients. There was significant correlation only between the change in CRP levels and change in FVC% ($r = 0.266$, $p = 0.008$) (Table 3).

DISCUSSION

This study showed that after a supervised eight-week protocol of moderate to high-intensity exercise

Table 3: The correlation between change in CRP levels and improved parameters after PR

Change in parameters	Correlation coefficient	p-value
Δ BMI (kg/m ²)	- 0.02	0.82
Δ FFMI (kg/m ²)	- 0.09	0.35
Δ MRC	- 0.00	0.95
Δ SGRQ-total	- 0.05	0.60
Δ FEV1% predicted	- 0.17	0.08
Δ FVC% predicted	- 0.266	0.008
Δ ISWT (meter)	- 0.14	0.14
Δ ESWT (min)	- 0.08	0.40

PR: Pulmonary rehabilitation; CRP: C-reactive protein; BMI: Body mass index; FFMI: Fat free mass index; SGRQ: St George's Respiratory Questionnaire; FEV1: Forced Expiratory Volume in one second; FVC: Forced vital capacity; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test

training program, there was a nonsignificant trend toward reduction in CRP levels. Even if our results are not enough to prove that the PR has significant anti-inflammatory effects, we can conclude that PR is unlikely to exacerbate systemic inflammation in COPD patients. This result is consistent with a recent study evaluating the effect of both acute exercise and PR on systemic inflammation^[17].

CRP and leukocytes are biomarkers of low-grade systemic inflammation and increased levels have been associated with poor prognosis^[18] and comorbidity^[2]. Relationships between CRP, IL-6, exercise tolerance and health status were found in different studies^[7,9]. It was also found that patients with COPD who walked the most had the lowest plasma CRP and IL-6 levels^[19]. Our study results also revealed a negative correlation between CRP levels and baseline exercise capacity in COPD patients. Unfortunately, no relationship was found between changes in CRP and exercise capacity after PR. Exercise training is the main component of the comprehensive rehabilitation programs^[20]. As patients with COPD demonstrate systemic inflammation at rest, exercise could further increase inflammatory mediators^[21] but resistance training has been shown to reduce muscle TNF- α in healthy older subjects^[22]. Exercise and rehabilitation in patients with COPD are likely to have similar anti-inflammatory effects^[23,24].

The intensity, duration and type of exercise can have a tendency to affect systemic inflammation markers^[12,13]. Jammes *et al* showed that IL-6 and TNF- α levels increased earlier and that the absolute change in cytokine levels was more noticeable in COPD patients than healthy controls after maximal cycling^[25]. However, in the study of Davidson *et al*, 20 COPD patients underwent incremental exercise and at the early time points after the end of exercise, a significant reduction in inflammatory cytokines was

shown^[26]. In a study in which 17 severe COPD patients with mean FEV1 predicted 40% instead of 75% as a constant-load exercise challenge, it has not found any increase in plasma IL-6 during or after exercise. This result has suggested that a certain level of exercise may be required to induce changes in systemic cytokine levels^[27]. In multiple studies which investigated the relationship between exercise and CRP in healthy subjects, it was found that a combination of aerobic and resistance training resulted in a significant reduction in CRP levels^[28-30], but exercise training has not been shown precisely to decrease the inflammation. In the studies after combined diet modification and exercise programs, CRP levels significantly decreased in healthy population. These findings suggested that weight loss by reduction in adipose tissue was important in reducing inflammation level, and combination of nutrition and exercise protocols should have been part of any lifestyle intervention program^[31]. In our study, a supervised, moderate to high intensity, combined aerobic and resistance exercise with nutritional recommendations reduced CRP level in COPD patients, although patients did not lose weight.

Several studies have demonstrated that concentration of CRP is increased in clinically stable COPD patients as compared to healthy controls^[2, 32-38]. In our study, even though most of the patients were severe and very severe, CRP levels were not high. In several studies, CRP and erythrocyte sedimentation rate was found to be negatively correlated with FEV1% in stable COPD patients^[36,18,39]. In a recent study, an inverse relation was demonstrated between the levels of CRP, TNF- α , IL-6, transforming growth factor beta (TGF- β), total leucocyte count and predicted FEV1%, while the strongest negative relation was with total leucocyte count^[17]. In a study of 938 COPD patients, lower FEV1 and FVC were correlated with the increase in CRP, IL-6 levels and the correlation between CRP and pulmonary function test was stronger in men than women^[4]. In another study, significant positive correlation was found between CRP and FVC%^[40]. In our study, even though the baseline CRP level and pulmonary function test results (FEV1, FVC) were not correlated, changes in FVC and CRP were correlated negatively. Decreased baseline inspiratory capacity was found to be associated with an increased serum CRP in stable COPD patients. According to this result, a relationship between dynamic hyperinflation and systemic inflammation was shown in advanced COPD^[41]. In our study, even though the results of lung volumes were missing, positive effect of exercise training on dynamic hyperinflation might also have a positive impact on CRP levels.

COPD is a systemic disease but other significant predictors of high CRP levels have been found to be related with age^[42], smoking pack-years^[43] and different comorbidities^[32,35,36]. Current smokers have higher CRP levels than nonsmokers^[44-46] and there was a positive association with the number of pack-years smoked^[47]. In our study, although all patients were ex-smokers, there was no correlation between pack-years of cigarette and CRP level. It has been previously found that older adults with COPD who had impaired physical function had higher concentrations of CRP and IL-6^[42], but we found no significant correlation between age and CRP levels.

Medical comorbidities are common among COPD patients. In an analysis of the prevalences of comorbidities associated with COPD, 32% had one additional condition, and 39% had two or more concurrent medical conditions^[48]. In our study, 36.5% of patients had one comorbidity (23.1% HT, 13.4% DM). Higher CRP levels were found in COPD patients with DM and cardiovascular disease^[49]. This study did not find any statistical difference in CRP levels of the patients having a comorbidity or not. In a recent meta-analysis, long term exercise was shown to reduce CRP levels in patients with DM^[46]. Exercise has been suggested to reduce inflammation by improving insulin resistance, as inflammatory markers are raised in insulin-resistant patients^[50]. It has also been observed that 6 months of exercise training reduced CRP levels by 35% in 43 middle-aged male and female participants at risk for cardiovascular diseases^[51]. In 235 patients with cardiovascular diseases, it was demonstrated that three months of exercise training reduced median CRP levels by 41% compared with no CRP changes in the control group^[52]. Likewise, we also observed a reduction in CRP levels after PR in patients with comorbid disease, but this did not reach statistical significance.

Limitations of the study can be listed as; 1) the absence of a control group, 2) CRP level was the only marker studied for inflammation status, 3) both only late response and acute response to exercise might have been investigated.

CONCLUSION

COPD patients with decreased exercise capacity had increased CRP levels. A long-term, supervised, moderate to high-intensity exercise training would have a positive impact on systemic inflammation in patients with or without comorbidities. After a multidisciplinary PR program, decreased CRP levels might foresee an improvement in lung functions by means of FVC%.

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Original Article

Predictive Parameters for Barrett's Esophagus: Percent Body Fat (PBF) and Visceral Fat Area (VFA) are more Valuable than Body Mass Index (BMI)

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ABSTRACT

Objective: It is well known that Barrett's Esophagus (BE) is an important precancerous lesion of esophageal adenocarcinoma. Gastroesophageal reflux is determined as pathophysiologic mechanism and obesity is the major etiologic factor. We aimed to investigate the quantifiable parameters of obesity and their role in development of BE.

Design: Patients were divided into two groups according to the presence or absence of BE, and records were compared intergroup.

Setting: A hospital data-based retrospective study designed in two-year time

Subjects: Patients who needed upper gastrointestinal endoscopic examination for various causes in general surgery and family practitioner out-patient clinics were included in the study.

Intervention: Upper gastrointestinal endoscopy

Main outcome measures: Body mass index (BMI), visceral fat area (VFA) and percent body fat (PBF) calculations were obtained by Body Composition Analyzer (BCA) and enrolled with age, gender, cigarette and alcohol habits, helicobacter pylori (HP) and BE findings.

Results: The median age was 47 (19 - 88) years and female/male ratio was 1.3 in 225 of patients who were included in the study. Twenty-five (11.1%) patients had BE. Tobacco usage raised BE occurrence ($p = 0.001$); but HP presence and alcohol habit were not effective ($p = 0.706$ and $p = 0.929$). BMI, PBF and VFA parameters were statistically higher in BE group ($p < 0.001$, $p = 0.001$ and $p < 0.001$). VFA had the highest sensitivity and specificity.

Conclusions: Smoking triggers BE but alcohol consumption or HP have no effectiveness. Obesity is the biggest problem; we found that PBF and VFA are more effective predictive parameters in development of BE

KEY WORDS: barrett's disease, body mass index, percent body fat, visceral fat area

INTRODUCTION

Barrett's Esophagus (BE) is the replacement of squamous mucosa by specialized intestinal columnar mucosa in the distal esophagus and it is known to be a precancerous state of esophagus adenocarcinoma^[1,2]. Although it was named by Norman Rubert Barrett (1903-1979), an Australian thoracic surgeon, in 1957; the histopathological changes were first described by Tileston in 1906^[3,4]. Although adenocarcinoma may occur without clinical signs of pre-existing reflux disease, about 60% of patients had this history^[5]. With the realization of this fact, investigations focused on

acid reflux through the esophagus from the stomach and its damage on squamous epithelial mucosa, and the predisposing conditions of this phenomenon. The prominent cause is obesity^[6-9]. We investigated obesity and BE association by quantitative markers. We also evaluated the effects of smoking, alcohol habits and helicobacter pylori (HP) infection on this phenomenon.

MATERIALS AND METHODS

According to Helsinki Declaration Criteria and after receiving the approval of the Local Ethics Committee, a hospital data-based, cross-sectional

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study was designed. The study area contained data of patients who were admitted to general surgery and family practitioner outpatient clinics of a university hospital and a state hospital. The patients who had epigastric pain, nausea/vomiting or retrosternal burning and the patients who needed control examination because of known peptic ulcer disease were admitted to outpatient clinics for investigation between December 2014 and January 2016. Upper gastrointestinal system endoscopic investigations were done, and body mass index (BMI), visceral fat area (VFA) and percent body fat (PBF) calculations were obtained by Body Composition Analyzer (BCA) (BCA X-Scan Plus II®, Jawon Medical, Korea) which works on the principles of bioelectrical impedance analysis. Age, gender, cigarette and alcohol habits; presence of HP and BE findings determined on upper gastrointestinal endoscopy; calculated BMI, VFA and PBF values by BCA; and the results of endoscopic biopsy specimens were enrolled. BE presence was demonstrated by histopathological examination on endoscopic tissue samples. The patients were divided into two groups according to the presence or absence of BE as Group I (G I) and Group II (G II). Fourteen patients were excluded from the study because of missing files, being under the age of 18, history of bariatric surgery or being unable to adjust to BCA device. BMI, PBF, VFA, tobacco and alcohol habits, presence of HP findings were compared intergroup.

Statistical Analysis

The data analysis was performed using SPSS for Windows, version 22 (SPSS 22, Chicago, IL, USA). The normality of the distributions of continuous variables was determined via the Kolmogorov-Smirnov test. The data were reported as mean \pm standard deviation for parametric tests or median and range for non-parametric tests where applicable. The differences between the data from the groups were compared via Student's t-test or the Mann-Whitney U test where appropriate. The categorical data were analyzed using Pearson's chi-square or Fisher's exact test where appropriate. Multiple linear regression analysis was used to assess the differences between groups in terms of age, gender, smoking, drinking alcohol, HP, VFA, BMI, and PBF. The coefficient of regression and the 95% confidence interval for each independent variable were also calculated. The cut-off values of parameters for discrimination of the groups were determined using the receiver operating characteristic (ROC) analysis. At each value, the sensitivity and specificity for each outcome under study were plotted, thus generating an ROC curve. A p-value < 0.05 was considered statistically significant.

RESULTS

The median age was 47 (19 - 88) years and the female to male ratio was 1.3 in 225 of patients who were included in the study. BE findings were found in 25 (11.1%) patients. Age and gender distributions were homogeny intergroup according to the presence or absence of BE ($p = 0.602$ and $p = 0.096$, respectively). Presence of HP and alcohol habit were not effective in development of BE ($p = 0.706$ and $p = 0.929$, respectively), but we found that smoking habit strongly triggered the occurrence of BE ($p = 0.001$). The demographic characteristics of the patients are

Table 1: Demographic characteristics of the patients

Characteristics	Group I (BE)	Group II (NBE)	All Patients	P value
Age	48 (20-79)	47 (19-88)	47 (19-88)	0.602
Gender (Male/Female)	7/18	91/109	98/127	0.096
Smoking Habit	11/25	48/200	59/225	0.032
Alcohol Habit	2/25	15/200	17/225	0.929
HP	11/25	96/200	107/225	0.706

BE: Barret's Esophagus; NBE: Non Barret's Esophagus; HP: Helicobacter Pylori

presented in Table 1. When we analysed BMI, PBF and VFA parameters, all of them were significantly higher in G I (with Barrett Disease) than G II (without Barrett Disease) ($p < 0.001$, $p = 0.001$ and $p < 0.001$). The distributions of BMI, PBF and VFA values in groups are seen in Figs 1 - 3 respectively. Under the ROC curves calculated cut-off values of BMI, PBF and VFA to predict the development of BE in groups, and sensitivity, specificity, positive predictive and negative predictive values are seen in Table 2 and Fig 4. According to these data, VFA parameters had the highest sensitivity and specificity.

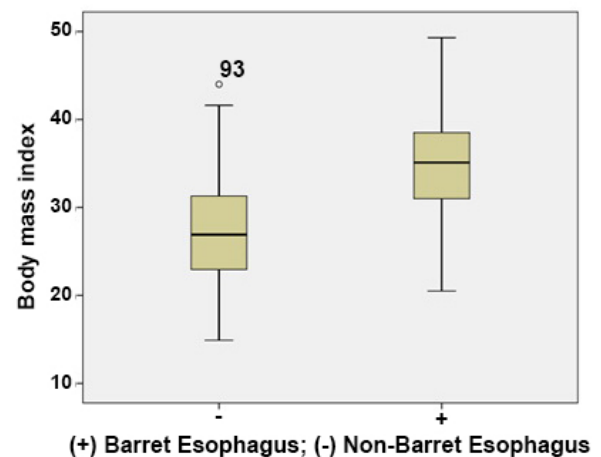


Fig 1: The distribution of Body Mass Index values in groups

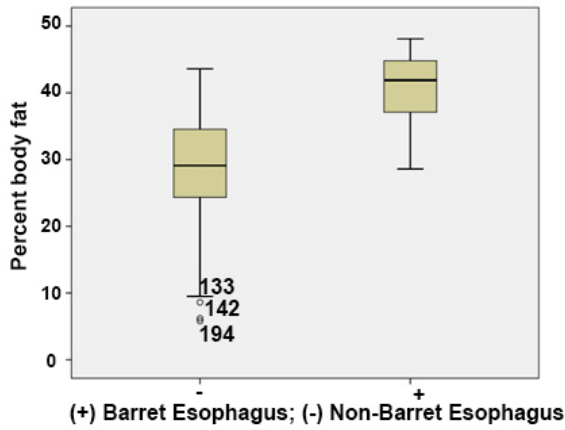


Fig 2: The distribution of Percent Body Fat values in groups

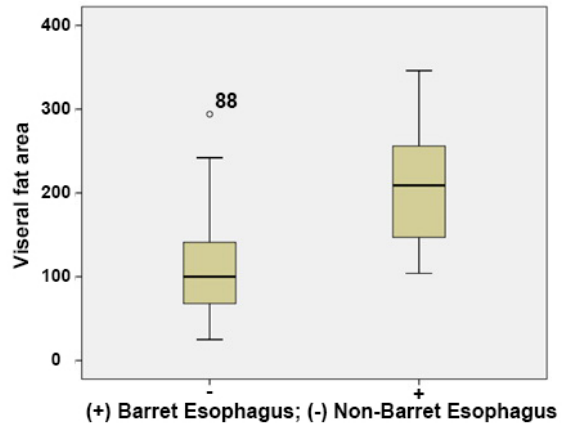


Fig 3: The distribution of Visceral Fat Area values in groups

Table 2: BMI, VFA and PBF parameters in groups

Parameters	Group I (BE)	Group II (NBE)	p-value	Cut off	Sensitivity	Specificity
BMI	35.1 (20.5 - 49.3)	26.9 (14.9 - 44.0)	< 0.001	30.85	0.760	0.740
VFA	209 (104 - 306)	100 (25 - 294)	< 0.001	145	0.760	0.775
PBF	41.9 (28.6 - 48.1)	29.1 (5.8 - 43.6)	< 0.001	36.15	0.800	0.815

BE: Barrett's Esophagus group; NBE: Non Barrett's Esophagus group; BMI: Body Mass Index; VFA: Visceral Fat Area; PBF: Percent Body Fat

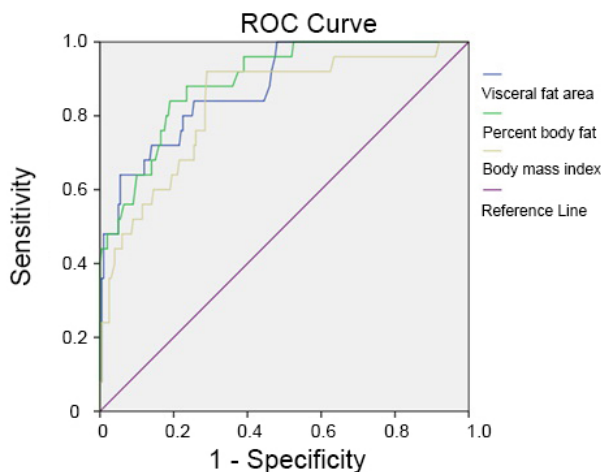


Fig 4: ROC curve graphic of the parameters

DISCUSSION

Intestinal metaplasia of the distal esophagus, also named BE, is considered to be a premalignant condition where metaplasia may progress to dysplasia and subsequently to adenocarcinoma^[1,10]. We found 25 (11%) of the patients had BE in 225 consecutive patient's study group which were examined by upper gastrointestinal endoscopy for various causes. This rate was higher than the average in literature. Endoscopically, the prevalence of BE has been estimated

at 1 – 2% in all patients receiving endoscopy for any indication, and anywhere from 5 - 15% in patients with symptoms of gastroesophageal reflux disease (GERD)^[11]. Perhaps our patients had predominantly reflux symptoms and peptic complaints, and screening examinations were minimal, so there may be a bias on this point. Comparing 25 patients with 200 can be considered as a limitation in our study. The number of patients were low due to cross-sectional retrospective feature of our study. Comparison was made between the patients with BE and the ones without during a certain period of time. Taking this into account and considering the literature data, 25 patients from a sample of 225 is a considerably high number.

There are several risk factors that raise acid reflux from stomach to distal esophagus and predispose BE. Some of them are genetic or structural and the others habitual or environmental. Fujita *et al*^[1] found that p53 over-expression was a risk factor for dysplasia of BE; on the other hand, high diastolic blood pressure might be protective. According to Duggan and co-workers study^[2], increasing homeostatic model assessment (HOMA) scores and increased leptin and insulin resistance were associated with increasing risk for BE, whereas increased level of high molecular weight adiponectin was inversely associated with BE. Thrift *et al*^[12] concluded that metabolic syndrome had additional risk of BE separate from obesity in their

work. Some studies emphasized male gender had a higher risk than females for BE in same conditions^[12,13]. There was no difference in our patients according to gender.

We found that there was no correlation between HP infection and BE ($p = 0.706$). In a 151-patient study, HP infection was found to be inversely associated with BE and might be protective^[1]. There was no exact explanation of this situation, but chronic and virulent HP infection may lead to gastric atrophy, resulting in suppression of acid production; and this may lower the risk of BE^[14].

In our series, smoking was found to be a predisposing factor for BE ($p = 0.001$). There were similar findings in several studies^[15-17]. However, some of the studies found no effect of this habit on BE development^[18,19]. Alcohol consumption had no trigger effect on BE development in our series ($p = 0.929$). There were similar results in the literature that support ours^[17,18,20,21].

Obesity with its trigger effect is the major research topic about BE in the literature^[6-9]. Generally, BMI was used to determine quantitative effect; but gastroesophageal reflux and obesity association and their effects on BE were controversial^[5,7,8,22-27]. There has even been an argument on the association between the length of BE and BMI. Abdallah *et al*^[28] demonstrated a correlation between BMI and the length of BE; but Nathanson *et al*^[29] found opposite results. We also found higher BMI values in patients with BE ($p < 0.001$). BMI can be calculated by the [weight (kg) / height² (cm)] formula. Recent studies have focused on visceral obesity rather than BMI^[13,30-33]. Visceral obesity is generally evaluated by measuring waist to hip ratio in these studies. More recently, bioelectrical impedance based methods have been used and these studies also emphasized the importance of abdominal obesity rather than total body fat^[34,35]. We evaluated patients by Body Composition Analyzer and enrolled the BMI, PBF and VFA output records. These parameters were statistically higher in BE group than non-BE group ($p < 0.001$, $p = 0.001$ and $p < 0.001$). Within these parameters, PBF and VFA are more effective in predicting development of BE than BMI with higher sensitivity and specificity.

CONCLUSION

It is known that higher BMI and history of smoking are risk factors for BE. In our study, we concluded that PBF and VFA are probably more effective predictive parameters in development of BE than BMI with higher sensitivity and specificity.

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Conflict of Interest: None

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Original Article

Frequency and Association of the Genetic Polymorphisms in Patients with Deep Venous Thrombosis and Healthy Subjects

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ABSTRACT

Objective: To compare the frequencies of factor V Leiden (FVL), prothrombin G20210A (PT G20210A), and methylenetetrahydrofolate reductase (MTHFR) polymorphisms in patients with deep venous thrombosis (DVT) and healthy controls

Design: A prospective case control study

Setting: Bozok University Hospital, Yozgat province, Turkey

Subjects: A total of 220 participants were accepted in the study (126 patients with DVT and 94 healthy blood donors). All participants were questioned regarding their medical history, and the diagnosis of DVT was based upon a physical examination, D-dimer testing, and a bilateral lower limb venous ultrasonographic examination. None of the 94 blood donors (control group) had any evidence of DVT.

Intervention: Polymerase chain reaction (PCR) and the amplification refractory mutation system were used to

identify the polymorphisms in the blood of the participants

Main outcome measures: The relationship between these polymorphisms and DVT was investigated

Results: Among the 126 DVT patients, FVL was present in 54 (42.8%), while FVL was found in only 18 (19.1%) of the 94 controls. The PT G20210A mutation was present in 13 patients (10.3%) and in 5 healthy controls (5.3%). The FVL and PT G20210A mutations were present at significantly higher rates in the patient group than in the healthy control group ($p < 0.05$). However, the MTHFR C677T and MTHFR A1298C polymorphisms were nearly equally distributed between the patients and controls.

Conclusion: FVL and PT G20210A polymorphisms contribute to the development of DVT and these may become clinically relevant when associated with other thrombophilic risk factors.

KEY WORDS: factor V, MTHFR, prothrombin, thrombophilia

INTRODUCTION

Deep vein thrombosis (DVT) is an important health problem worldwide. After ischemic heart disease and stroke, DVT is the third most frequent cardiovascular system disorder, affecting 0.1% of the elderly population^[1,2]. Its pathophysiology is multi-causal, and involves hereditary and acquired risk factors^[3,4].

Multiple complex interactions among acquired, environmental, and genetic factors can alter the equilibrium between procoagulant and anticoagulant mechanisms, which can lead to venous thromboembolism^[5,6]. The single nucleotide

polymorphisms in the genes encoding coagulation factors change the delicate balance in the hemostatic system in favor of thrombosis^[7].

In 1993, Dahlback *et al*^[8] uncovered a previously unrecognized mechanism for thromboembolism. This mechanism is characterized by a poor anticoagulation response to activated protein C (APC), which is caused by a polymorphism of factor V (FV). In this polymorphism, arginine is replaced by glutamine, which inhibits the cleavage of factor V by APC^[7]. This mutant molecule, known as factor V Leiden (FVL), is the most commonly detected hereditary thrombophilic

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risk factor leading to DVT (due to its resistance to APC)^[1,2].

Prothrombin gene polymorphism (PT G20210A) results in increased levels of prothrombin, which creates a higher predisposition towards thrombophilia^[9]. This polymorphism, which is within the 3' untranslated region of the prothrombin gene (mutation of a G to an A at position 20210) was first identified by Poorts and colleagues^[10] in 1996. Carriers of PT G20210A have higher plasma prothrombin concentrations than control subjects, which gives them an increased risk of venous thrombosis^[10].

The enzyme methylenetetrahydrofolate reductase (MTHFR) is involved in homocysteine metabolism. The MTHFR C677T polymorphism has been shown to cause increased homocysteinemia levels, leading toward a tendency to thrombosis. It is suggested that the MTHFR C677T polymorphism has little effect on its own, but has synergy with the FVL mutation to cause a predisposition to venous thromboembolism^[11].

The current study aimed to compare the frequencies of FVL, PT G20210A, and MTHFR polymorphisms in patients with DVT and healthy controls.

SUBJECTS AND METHODS

The study was performed at Bozok University Hospital in Yozgat, Turkey between April 2013 and January 2016. An informed consent was taken from all of the participants, and this study was accepted by the ethics committee of Bozok University (58/604-176).

A total of 220 participants were accepted in the study (126 patients with DVT and 94 healthy blood donors). Patients with secondary DVT were excluded from the study.

All participants were questioned regarding their medical history, and the diagnosis of DVT was based upon a physical examination, D-dimer testing, and a bilateral lower limb venous duplex ultrasonographic examination. None of the 94 control subjects had any evidence of DVT. Protein C, protein S, and antithrombin deficiency could not be evaluated due to patients having been on anticoagulant therapy.

Ten milliliters of peripheral venous blood was drawn from each participant into an ethylenediaminetetraacetic acid (EDTA) tube. DNA was extracted from the peripheral blood samples by kit methods. Polymerase chain reaction (PCR) and the amplification refractory mutation system were used to identify FVL, PT G20210A, MTHFR C677T, and MTHFR A1298C. Polymorphism screening was carried out with a SNaPshot® multiplex system (Applied Biosystems Inc., Switzerland). Wild, heterozygous, and homozygous genotypic distributions of these polymorphisms were defined as numbers and percent frequencies.

DVT treatment was initiated with low molecular weight heparin (LMWH) and oral warfarin, and was continued for at least five days until targeted international normalized ratio (INR) values (between 2 and 3) were obtained for at least two consecutive measurements. Then, LMWH therapy was discontinued, and oral warfarin therapy was continued for at least six months. Twelve patients did not reach their targeted INR values, and therefore, they were treated with rivaroxaban.

Statistics

Results are reported as means ± standard deviations (SD). The prevalence of polymorphisms is shown as percentages (%). For statistical analyses, independent samples t- tests and chi-square tests were used. Values of $p < 0.05$ were accepted as significant.

RESULTS

In the DVT patient group, there were 72 males and 54 females ranging in age from 22 to 83 years, with a mean age of 50.3 ± 15.7 years. In the healthy group, there were 42 males and 52 females ranging in age from 17 to 78 years with a mean age of 47.5 ± 14.1 years.

DVT was diagnosed in the left lower limb of 63 patients (50%), in the right lower limb of 50 patients (39.7%) and in both lower limbs of 13 patients (10.3%). DVT was localized at the iliofemoral segment in 42 patients (33.3%), at the femoropopliteal segment in 66 patients (52.4%), and at the infra-popliteal segment in 18 patients (14.3%).

The FVL genotypes were found in 54 (42.8%) patients and in 18 (19.1%) healthy controls. The heterozygous and homozygous FVL genotypes were identified in 43 (34.1%) and 11 (8.7%) patients, respectively (Table 1). There were no homozygous carriers for either FVL or PT G20210A mutations in the healthy controls (Table 2). Patients with DVT had a significantly higher frequency of FVL than the healthy

Table 1: Distribution of the polymorphisms in patients with DVT

Polymorphism	Male	Female	p-value	Total n (%)
HET FVL	26	17	0.041	43 (34.1)
HOM FVL	8	3	0.032	11 (8.73)
HET PT G20210A	6	6	NS	12 (9.53)
HOM PT G20210A	0	1	NS	1 (0.8)
HET MTHFR C677T	22	18	NS	40 (31.7)
HOM MTHFR C677T	7	2	0.026	9 (7.1)
HET MTHFR A1298C	37	24	NS	61 (48.4)
HOM MTHFR A1298C	11	6	NS	17 (13.4)

FVL: Factor V Leiden; PT 20210A: Prothrombin gene mutation; MTHFR: Methylenetetrahydrofolate reductase; HET: heterozygous; HOM: homozygous; NS: non-significant ($p > 0.05$)

Table 2: Distribution of the polymorphisms in healthy subjects

Polymorphism	Male	Female	p-value	Total n (%)
HET FVL	10	8	NS	18 (19.1)
HOM FVL	0	0	NS	0
HET PT G20210A	3	2	NS	5 (5.3)
HOM PT G20210A	0	0	NS	0
HET MTHFR C677T	15	16	NS	31 (32.96)
HOM MTHFR C677T	3	5	NS	8 (8.51)
HET MTHFR A1298C	20	27	NS	47 (50)
HOM MTHFR A1298C	7	7	NS	14 (14.9)

FVL: Factor V Leiden; PT 20210A: Prothrombin gene mutation; MTHFR: Methylenetetrahydrofolate reductase; HET: heterozygous; HOM: homozygous; NS: non-significant ($p > 0.05$)

group ($p < 0.05$). Further, the FVL polymorphism was more frequently encountered in males in the DVT group (47.2% males vs. 18.5% females) and in the control group (21.1% males vs. 15.4% females), revealing an association between male gender and venous thrombosis ($p < 0.05$).

The PT G20210A genotypes were detected in 13 (10.3%) patients and 5 (5.3%) healthy participants. Five patients (5.3%) and 1 healthy control (1%) had both the FVL and PT G20210A polymorphisms. The distribution of the co-existence of the PT G20210A mutation with other mutations among patients and healthy controls is presented in Tables 3 and 4.

Table 3: Distribution of the accompanying additional polymorphisms in 13 DVT patients with PT G20210A polymorphism

PT G20210A	FVL	MTHFR C677T	MTHFR A1298C
HOM	WT	WT	WT
HET	HET	WT	WT
HET	WT	WT	HET
HET	WT	HOM	WT
HET	WT	WT	HET
HET	WT	WT	WT
HET	WT	WT	HET
HET	HET	WT	HET
HET	WT	HOM	WT
HET	HOM	WT	HOM
HET	HET	HET	WT
HET	HET	HET	WT
HET	WT	HET	WT

FVL: Factor V Leiden; PT 20210A: Prothrombin gene mutation; MTHFR: Methylenetetrahydrofolate reductase; HET: heterozygous; HOM: homozygous; WT: wild type

The homozygous and heterozygous MTHFR C677T polymorphisms were found in 9 (7.1%) and 40 (31.7%) patients respectively, and in 8 (8.5%) and 31 (32.9%) healthy controls, respectively. The homozygous and heterozygous MTHFR A1298C polymorphisms were present in 17 (13.4%) and 61 (48.4%) patients

Table 4: Distribution of the accompanying additional polymorphisms in five healthy controls with heterozygous PT G20210A polymorphism

PT G20210A	FVL	MTHFR C677T	MTHFR A1298C
HET	WT	HET	HET
HET	WT	HET	WT
HET	HET	HET	WT
HET	WT	HOM	WT
HET	WT	WT	HET

FVL: Factor V Leiden; PT 20210A: Prothrombin gene mutation; MTHFR: Methylenetetrahydrofolate reductase; HET: heterozygous; HOM: homozygous; WT: wild type

respectively, and in 14 (14.9%) and 47 (50%) healthy controls, respectively. The MTHFR C677T and MTHFR A1298C polymorphisms were nearly equally distributed between both groups. However, the combination of MTHFR C677T and FVL was detected in 23 (18.2%) patients with DVT and in 6 (6.3%) healthy individuals ($p < 0.05$). Similarly, the combination of MTHFR A1298C with FVL was significantly higher in patients as compared to controls (37 (29.3%) patients and 11 (11.7%) controls, respectively).

DISCUSSION

In the past five decades, the biomolecular bases of both the coagulant and anticoagulant pathways have been clarified, and several inherited thrombophilic risk factors have been identified^[12]. The three most common inherited risk factors known to predispose patients to venous thrombosis are FVL, PT G20210A, and MTHFR C677T.

The heterozygous and homozygous FVL polymorphisms increase the risk of venous thrombosis between 3 and 7-fold and between 50 and 100-fold respectively^[13]. Although the prevalence of the FVL polymorphism is higher in Caucasians compared with the Asian and African populations, recent Asian studies have reported different results. Irani-Hakime *et al*^[13] reported that frequencies of FVL are almost the same in eastern and western countries. Further, Saeed *et al*^[3] suggests that the FVL polymorphism is not rare in the Asian population.

Epidemiological and biochemical investigations support evidences that FVL should have occurred as a single event in the past. Its prevalence is considerably higher in the Mediterranean region compared to the rest of the world^[9]. Turkey lies between the Mediterranean basin and Eurasia. Thus, one would expect a high frequency of the FVL polymorphism among the Turkish people. The FVL frequency was reported to range between 3.5% and 15% in healthy Turks^[14]. A meta-analysis performed in Turkey

revealed an association between FVL and venous thrombosis^[15]. In that study, the pooled frequency of FVL was significantly higher in patients with venous thrombosis (22.8%) compared with controls (7.6%)^[15]. Hotoleanu *et al*^[16] and Coen *et al*^[17] reported that DVT patients have a significantly higher prevalence of FVL than healthy controls (13.8% vs. 2.7% and 21% vs. 4%, respectively). In the current study, the FVL polymorphism was found in 42.8% of DVT patients and in 19.1% of healthy participants.

The association of two or more hereditary thrombophilic defects in addition to the FVL mutation further increases the risk and severity of venous thrombosis^[4]. The life-long risk of symptomatic venous thromboembolism (VTE) in heterozygous FVL carriers is approximately 10%; this polymorphism is present in up to 37% of patients with post-thrombotic syndrome^[4]. Therefore, we suggest that healthy FVL carriers, especially those with other associated hereditary thrombophilic defects, should be closely monitored as long as they live. These healthy carriers should undergo prophylactic measures against acquired risk factors, including the surgery (especially orthopedic surgical interventions), immobilization, trauma, long-distance air travel, and pregnancy.

The PT G20210A mutation is relatively uncommon, and has been found in 1 - 2% of the worldwide population. Similar to the FVL polymorphism, the PT G20210A polymorphism appears to be specific to Caucasian populations^[18]. The risk of venous thrombosis increases considerably in those with both the PT G20210A and FVL polymorphisms^[19]. The risk of venous thrombosis increases 2 - 3 fold for those with the PT G20210A genotype alone and this risk increases 20-fold for those with mutations in both PT G20210A and FVL^[20]. A previous study reported that the PT G20210A mutation was detected in 5 - 17% of patients with venous thrombosis^[21]. In our current study, the PT G20210A polymorphism was more frequently detected in the DVT group (10.3%) than in the control group (5.3%), revealing a significant association of DVT with the PT G20210A polymorphism ($p < 0.05$).

The FVL and PT G20210A polymorphisms seem to be considerably higher frequency than other hereditary thrombophilic risk factors^[6]. Both polymorphisms are very frequent in Caucasian people and are associated with an increased risk of venous thrombosis^[1]. The prevalence of FVL and PT G20210A varies in different ethnic groups and geographical regions^[22]. In the current study, FVL and PT G20210A were detected in 42.8% and 10.3% of patients with DVT respectively, indicating a significant association between these polymorphisms and DVT. Similarly, in patients with VTE, these two common mutations were found to be

higher in other Turkish populations^[6]. Therefore, both the FVL and PT G20210A genotypes are important risk factors for the development of DVT in Turks.

Administration of birth control pills increases the risk of VTE 16-fold in heterozygous PT G20210A carriers and 20 - 35 fold in heterozygous FVL carriers^[20]. In our current study, the two healthy controls that had the FVL mutation were instructed not to continue taking birth control pills in order to avoid possible thrombotic complications.

Homozygous MTHFR C677T carriers appear to have hyperhomocysteinemia when their folic acid intake is insufficient. Unlike homozygous MTHFR C677T carriers, homozygous MTHFR A1298C carriers are not associated with increased homocysteinemia levels^[23].

Although homozygous MTHFR A1298C carriers do not tend to have hyperhomocysteinemia, Kreidy *et al*^[19] suggest that patients with extended venous thrombosis that is resistant to anticoagulant therapy and not explained by the most usual polymorphisms should be screened for the MTHFR A1198C polymorphism. The frequency of the MTHFR A1298C polymorphism has not been as well studied as that of the MTHFR C677T polymorphism. The frequency of homozygous MTHFR A1298C carriers has been reported as approximately 9% in Canadian and Dutch populations, and as 10% in Turkey^[24]. In our current study, the frequency of the homozygous MTHFR A1298C mutation was 14.9% in the healthy controls and 13.4% in the DVT patients.

According to a comprehensive study, there is no rationale for detecting the MTHFR C677T polymorphism as a thrombophilic risk factor^[25]. Therefore, when present alone, these genotypes do not seem to be risk factors for DVT. In the current study, the frequencies of homozygous MTHFR C677T were similar in patients and healthy subjects (7.1% vs. 8.5% respectively). However, the concomitant presence of FVL and double heterozygous polymorphisms of MTHFR C677T/A1298C was found in 11 patients (8.7%) and in 2 healthy controls (2.1%), showing a significant association with deep venous thrombosis.

CONCLUSION

The results of this study reveal that the frequencies of the FVL and PT G20210A polymorphisms were significantly higher in patients with DVT than those in healthy participants. Thus, the FVL and PT G20210A polymorphisms most likely play a contributory role in the development of DVT. In contrast, the MTHFR C677T and MTHFR A1298C genotypes were not associated with a predisposition to the development of DVT. However, a combination of double heterozygous polymorphisms of MTHFR C677T/A1298C with

FVL may be associated with an increased risk of DVT. Further studies should be performed in order to confirm the importance of these combinations as hereditary risk factors for the development of DVT.

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Original Article

Short Term Results of Laparoscopic Decortication of Simple Renal Cysts using Harmonic Scalpel

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ABSTRACT

Objective: The current study aimed to report the efficacy and safety of harmonic scalpel for laparoscopic renal cyst decortication

Design: Retrospective study

Setting: Department of Urology, Hitit University, Corum Training and Research Hospital, Turkey

Subjects: Thirty four patients with renal cyst

Intervention: Laparoscopic decortication

Main outcome measures: The symptoms at presentation and recurrence were recorded

Results: Thirty-five patients (21 males and 14 females) were included in the study. The patients' ages were between 30 and 77 years with a mean of 57.51 ± 11.65 years. The cysts' size was between 45 and 105 mm with a

mean of 75.62 ± 18.07 mm. Retroperitoneal approach was performed in three patients. The mean follow up period was 13.94 ± 9.7 months. Bleeding occurred in one patient in the post-operative period. One patient had a history of percutaneous cyst aspiration before. Pathological examination revealed benign results in all patients. Three patients had recurrence in radiological imaging studies without symptom in follow-up period. Surgical success was defined as no recurrence of the renal cyst and a decrease or disappearance of the pain after the operation, which was achieved in 90.62% of the patients.

Conclusion: Harmonic scalpel is an effective and safe method for decortication of a renal cyst with a high success rate.

KEY WORDS: bosniak, cysts, kidney diseases, kidney neoplasms, laparoscopy

INTRODUCTION

Simple renal cyst is a common benign disease in the adult population, which accounts for 50% of adults^[1]. Most of the simple renal cysts are only diagnosed incidentally. The most common symptoms and complications are flank pain, hypertension, hematuria, recurrent urinary infection, compressive collecting system obstruction and renal failure^[2]. While there are these symptoms and/or complications, treatment is needed^[1].

Ultrasonography and computed tomography are usually used to diagnose renal cysts. Ultrasonography is an imaging system that has more advantages for convenience and cost than computed tomography. Renal cysts were classified as Bosniak type I and II (simple), IIF, III and IV (complex). While simple cysts do not require intervention unless symptomatic,

complex cysts must be treated, and Bosniak IIF needs follow-up.

The current treatment procedures of simple renal cysts are aspiration with or without sclerotic agents, laparoscopic surgery, robotic surgery and open surgery^[3]. Laparoscopic renal cyst decortication by transperitoneal or retroperitoneal is the most preferred procedure for symptomatic renal cysts^[1].

The current study aimed to report safety and efficacy of harmonic scalpel (Ethicon) for decortication of simple renal cyst in the short term follow-up.

SUBJECTS AND METHODS

A total of 37 patients with renal cyst who were treated with laparoscopic surgery between September 2013 and May 2016 were evaluated. Two patients were excluded from the study due to the

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Fig 1: Laparoscopic image of the renal cyst

use of monopolar coagulation devices. All patients were diagnosed by ultrasonography and computed tomography with intravenous contrast. Percutaneous cyst aspiration had been performed in one patient previously. According to the Bosniak classification, 30 patients were Bosniak type I and 4 patients were type II. One of the patient's cyst was suspicious for communication with pelvicalyceal system. Retrograde ureteropyelography confirmed no communication. All the patients were followed up at regular intervals after the operation. Post-operative symptoms were evaluated and radiological examinations with ultrasonography or computed tomography were used 1 month after the surgery. Surgical success was defined as no recurrence of the renal cyst and decrease or disappearance of the pain after the operation. Transperitoneal (n = 32) and retroperitoneal (n = 3) approaches with three ports were used (11 mm for camera and two 5 mm trocars). The operations were performed under general anesthesia in the lateral decubitus position. For the retroperitoneal approach, a skin incision was made over the midaxillary line between the 12th rib and iliac crest. After blunt dissection with a finger, the retroperitoneal space was entered. A balloon dilatator was used for working space. The other trocars were inserted in the anterior axillary line and posterior axillary line inferior to the 12th rib after pneumoretroperitonum was established. The transperitoneal technique was performed both with a Veress needle and open techniques. The first trocar was inserted near the umbilicus and two trocars were inserted according to the cyst localization (Fig 1). Harmonic scalpel (Ethicon) was used to mobilize the colon, incision of adhesions and cutting the cyst wall from the kidney in the transperitoneal approach and to dissect Gerota fascia and cutting the cyst wall in the retroperitoneal technique (Fig 2).

Data analysis was conducted using the Statistical Package for the Social Sciences 19.0 (SPSS Inc., Chicago,



Fig 2: Laparoscopic image after complete excision of the cyst with Harmonic scalpel

IL). The patients' age and cyst size were expressed as mean \pm standard deviations.

RESULTS

Table 1 shows the characteristics of the patients. Thirty five patients were included in the study. Clinical presentation of patients were flank pain (n = 28), hypertension (n = 6) and collecting system obstruction (n = 1). Three patients had a diagnosis of polycystic renal disease and laparoscopic decortication was performed for the pain. Retroperitoneal laparoscopic approach was performed in three patients. Pneumoperitoneum was achieved by a Veress needle in 8 patients and by open technique in 24 patients. All of the patients' pathological results were normal. The peri-operative and post-operative data are shown in

Table 1: The characteristics and clinical findings of the patients

Variables	n (%)
Number of patients	35 (100)
Male	21 (60)
Female	14 (40)
Age (Mean \pm SD, range)	57.51 \pm 11.65 (30 - 77)
Laterality	
Right	19 (54.28)
Left	16 (45.71)
Localization	
Upper	13 (37.14)
Middle	10 (28.57)
Lower	8 (22.85)
Posterior	3 (8.57)
Medial	1 (2.85)
Mean \pm SD diameter (mm)	75.62 \pm 18.07
Clinical Presentation	
Flank Pain	28 (80)
Hypertension	6 (17.14)
Collecting system obs	1 (2.85)

Table 2: Peri-operative and post-operative parameters

Parameters	n (%)
Access	35 (100)
Transperitoneal	32 (91.42)
Retroperitoneal	3 (8.57)
Mean duration of operation (min)	50.85 ± 31.16
Success rate (%)	90.62*
Duration of hospitalization (days)	1.25 ± 1.03
Follow-up (months)	13.94 ± 9.70
Pneumoperitoneum	32 (100)
Veress needle	8 (25)
Open technique	24 (75)
Conversion to open surgery	0 (0)

*Three patients were excluded for polycystic renal disease (29/32)

Table 2. Bleeding occurred in one patient in the post-operative period. One month after the surgery, all patients were followed up. The symptom of pain was questioned and renal ultrasonography was done in the first month. Three patients had recurrence of renal cyst in the follow-up period.

DISCUSSION

The incidence of renal cyst increases with age, but most of the patients are asymptomatic^[4]. The prevalence of simple renal cyst is more than 5% in the age of 40's and 36% in the 80's and renal cyst is often diagnosed incidentally^[5]. The majority of simple renal cysts are benign and diagnosed with ultrasonography or computed tomography that have been widely used in daily urology practice^[3]. Sexual differences of renal cyst has variable results in the studies^[6-9]. Chin *et al* and Terada *et al* reported that the prevalence rates are higher in males than females^[6,7]. On the contrary, Park *et al* and Yamagishi *et al* reported that there were similar prevalence rates between the two sexes^[8,9]. In the present study, most of the patients (60%) were male. Clinical presentations of renal cyst include back pain, urinary tract infection, hemorrhage, compressive collecting system obstruction, hematuria, and hypertension. The renal cysts that cause symptoms or complications needed treatment. The main target for the treatment is to excise the cyst wall, evacuate its fluid contents to decompress the renal parenchyma and prevention of recurrence. Open surgery was the only treatment choice before the 1980s^[10]. Percutaneous aspiration was the primary treatment in the early 1970s^[4]. Ethanol was used as the sclerosing agent for renal cyst in 1981^[11]. The other agents for sclerotherapy are glucose, pantopaque, bismuth phosphate, phenol, ethanolamine oleate, quinacrine hydrochloride, morrhuate sodium, tetracycline, minocycline and OK-432^[3]. Percutaneous aspiration is a minimally invasive method, but has a very high recurrence rate (up to

90%). Although many different sclerosant agents have been reported for renal cysts, the recurrence rate is high (54%). Additionally, there is a risk of collecting system strictures due to the extravasation or inadvertent instillation of the sclerosant agent into the retroperitoneum. Percutaneous decortication and indirect percutaneous access have also been described^[1]. Laparoscopic decortication of renal cyst was first described by Hulbert *et al* in 1992^[12]. The technique is the first choice for treatment of simple renal cyst. Laparoscopic decortication is less invasive and safer than open surgery, but more invasive than percutaneous techniques. The recurrence rate for laparoscopic decortication is about 19% at the follow-up of 67.2 months, which is far lower than percutaneous aspiration (54%) with sclerosant agent^[13]. New energy sources were established for laparoscopic operations. Monopolar energy has the advantage of cost and availability, but the disadvantage of thermal damage^[2]. The bipolar systems such as plasmakinetic and Ligasure for decortication of renal cysts were reported in the literature. The Harmonic scalpel (Ethicon) is approved for sealing vessels up to 5 mm by the Food and Drug Administration^[14]. The Harmonic scalpel (Ethicon) uses piezoelectric ceramic converting electrical impulses to mechanical energy at the active tip that vibrates at 55,000 cycles per second and can be set at various excursion distances for modification of cutting and coagulation.

Tefekli *et al* reported a radiological success rate of 88.2% and symptomatic success rate of 89.5% with bipolar plasmakinetic system^[15]. Erdem *et al* reported a radiological success rate of 100% and symptom success rate of 94.2% with Ligasure when followed up at 12.5 months^[2]. To my knowledge; there is only one study for laparoscopic renal cyst decortication using the Harmonic scalpel (Ethicon)^[16]. In this study, McNally *et al* reported that the symptomatic success was 100% in patients (n = 7) with polycystic renal disease. The radiological and symptomatic success rates are 90.62% in this study. The patients with polycystic renal disease were not included for the success rate because of the nature of the disease. I think that the recurrence may have occurred because of low tissue excision and/or radiological failure.

Cost of the Harmonic scalpel (Ethicon) was approximately 1000 US dollars in the beginning of the study. The price of the device decreased to about 400 US dollars in 2016. For developing countries, I think that price (1000 US dollars) is very expensive for simple renal cyst treatment but now the price is cheaper than at the beginning of the study. I suggest the Harmonic scalpel (Ethicon) for surgeons with low experience in laparoscopy.

CONCLUSION

Laparoscopic decortication of simple renal cyst is an effective treatment with low recurrence rate. Using Harmonic scalpel (Ethicon) is safe for laparoscopic renal cyst decortication with high success rate.

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Original Article

Clinical Differences between Predominantly Fat Increase and Muscle Increase Subtypes of Thyroid Eye Disease in Chinese Patients

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ABSTRACT

Objective: To compare the clinical differences between the subtypes of thyroid eye disease, involving predominant fat increase and muscle increase

Design: Retrospective, observational case series

Setting: Zhongshan Ophthalmic Center

Subjects: Thirty-six patients with thyroid eye disease

Intervention : None

Main outcome measures: Main characteristics of predominant fat increase and muscle increase subtypes in thyroid eye disease

Results: The patients with predominantly fat increase were younger (median: 25 vs. 51 years, $P = 0.007$), had larger exophthalmometry values (median: 23 vs. 21.5 mm, $P = 0.049$) and much longer duration of exophthalmos (median: 60 vs. 6.5 months, $P < 0.001$), but lower clinical activity scores (median: 0.5 vs. 2, $P =$

0.005), compared to those patients with predominant muscle increase. The subtype with predominant fat increase had a smaller percentage of dysthyroid optic neuropathy than the subtype with predominant muscle increase (12.5% [1/8] vs. 79% [22/28], $P < 0.001$). In the predominant fat increase subtype, the corrected visual acuity in the one eye with dysthyroid optic neuropathy was 0.4. In the predominant muscle increase subtype, the median corrected visual acuity in the eyes with dysthyroid optic neuropathy was 0.15.

Conclusions: There are distinct differences between Chinese thyroid eye disease patients with predominant fat increase and muscle increase subtypes. In the predominant fat increase subtype, dysthyroid optic neuropathy rarely occurs, and visual loss caused by dysthyroid optic neuropathy tends to be relatively mild.

KEY WORDS: dysthyroid optic neuropathy, fat predominant subtype, Graves' ophthalmopathy, muscle predominant subtype, thyroid-associated ophthalmopathy

INTRODUCTION

Thyroid eye disease (TED) is an autoimmune disease characterized by a variety of clinical features including pain, gritty eyes, photophobia, chemosis, diplopia, and exophthalmos^[1-4]. According to literature, up to 5% of patients with TED are affected by dysthyroid optic neuropathy (DON), a potentially blinding complication^[5,6].

TED has two "abnormal" subtypes: subtype 1, with a predominant increase in fat volume, and subtype 2, with a predominant increase in muscle

volume. Regensburg *et al* found distinct differences between these two subtypes in European patients^[7]. In a study by Rootman^[8], however, several variations between Asians and Caucasians with TED were highlighted. Asians with TED have less muscle involvement but more apical compression^[8]. Therefore, the findings in European population may not be completely generalizable to the Chinese population. The current study aimed to investigate the clinical differences between these two subtypes of TED among Chinese patients.

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SUBJECTS AND METHODS

Using a retrospective consecutive case series design, patients with TED admitted to the Department of Orbital Disease and Ocular Tumors at the Zhongshan Ophthalmic Center, Sun Yat-sen University, between September 2010 and November 2012 were evaluated. TED diagnoses were determined based on Bartley's criteria^[9]. The patients were classified according to the NOSPECS classification (No signs and symptoms (Score 0), Only signs (Score 1), Soft tissue involvement (Score 2), Proptosis (Score 3), Extraocular muscle involvement (Score 4), Corneal involvement (Score 5), and Sight loss (Score 6))^[10], and the 7-point modified clinical activity score was applied^[11]. DON was categorized according to the criteria proposed by Dayan *et al*^[12]. This retrospective study was approved by the institutional review board of Zhongshan Ophthalmic Center and followed the tenets of the Declaration of Helsinki. All patients provided written consent.

Patients were included if they were Chinese and ≥ 18 years old, underwent an orbital magnetic resonance scan with axial and coronal views within three weeks after presentation in our center, and had no overt hypo- or hyperthyroidism when presented. Patients were excluded if they had received previous orbital surgery, had ocular trauma, or had primary ocular diseases that may affect the assessment of visual function (except keratopathy and optic neuropathy related to TED). Based on MRI scans, two ophthalmologists (Y.D. and H.Y) identified whether an orbit selected randomly in a patient has predominant fat increase subtype or predominant muscle increase subtype.

Data obtained from each patient included the following variables: age, gender, corrected decimal visual acuity, intraocular pressure (as measured using a non-contact tonometer), exophthalmometry (as measured using a Hertel exophthalmometer), subjective diplopia, the NOSPECS classification, and the clinical activity score. Corneal and optic disc appearances were also evaluated.

Eyes without form vision were assigned decimal equivalents as follows: counting fingers = 0.00500; hand motions = 0.00250; light perception = 0.00125; and no light perception = 0.00010^[13]. The corrected decimal visual acuities were converted to the logarithm of minimal angle of resolution (LogMAR) scores for statistical analysis.

Statistical analyses were performed using SPSS 13.0 for Windows (SPSS, Chicago, IL, USA). Fisher's exact test and the Mann-Whitney *U* test were used to analyze the differences between the predominant fat increase and muscle increase subtypes of TED, as

appropriate. The relationships among gender, age, clinical activity score, and DON were evaluated using the Spearman rank order correlation. $P < 0.05$ was considered significant.

RESULTS

Out of 98 consecutive cases with TED, 2 cases were excluded: 1 case had severe pterygium, glaucoma and age-related cataracts; and the other case had previous ocular trauma. Eight cases were identified as the predominant fat increase subtype, 28 cases as predominant muscle increase.

When we compared clinical characteristics between the predominant fat increase and muscle increase subtypes, there were no differences in gender, diplopia, optic disc morphology, and keratopathy. However, the percentage of DON in the predominant muscle increase subtype was significantly higher than the percentage in the predominant fat increase subtype ($P < 0.001$) (Table 1). In general, DON did not correlate with gender ($r = 0.084$, $P = 0.626$) but did correlate with age ($r = 0.617$, $P < 0.001$) and clinical activity score ($r = 0.581$, $P < 0.001$). Also, duration of exophthalmos correlated negatively with clinical activity score ($r = -0.378$, $P = 0.025$).

In the predominant muscle increase subtype, 22 cases (13 female and 8 male) with definite DON had a median corrected visual acuity of 0.15 (equal to 20/133) (range: no light perception to 0.8). In the predominant fat increase subtype, the only case (female) with definite DON had a corrected visual acuity of 0.4 (equal to 20/50).

DISCUSSION

Compared to the predominant muscle increase subtype, patients with the predominant fat increase subtype tended to be much younger ($p = 0.007$) and to have much milder visual loss ($p = 0.004$). Although patients with the predominant fat increase subtype had more severe exophthalmos ($p = 0.049$), the subtype had a much lower percentage of DON ($p < 0.001$). The predominant fat increase subtype of TED is much less common, accounting for only 8.3% (8/96) of the patients in our study and 5.3% (5/95) of the patients in the study by Regensburg *et al*^[7].

The predominant fat increase subtype appears to take place in an earlier stage of the TED than the predominant muscle increase subtype. If this hypothesis is true, all the TED cases would undergo the stage of fat increase. In our study, however, only 8.3% (8/96) of patients are fat predominant group. They had less activity of the disease. It seems that such fat or muscle phenotype has been determined at the beginning of TED by fibrocytes, which can differentiate

Table 1: Comparison of clinical features between the subtypes of thyroid eye disease involving an increase predominant in fat or muscle in this study

Variables	Predominant fat increase subtype	Predominant muscle increase subtype	p-value
Gender			0.115 *
Female (n)	7/8	15/28	
Male (n)	1/8	13/28	
Age (years)	25 (19 - 58)	51 (32 - 65)	0.007 †
Intraocular pressure	15 (14 - 20)	20 (15 - 55)	0.009 †
Subtotal thyroidectomy			0.555 *
Yes (n)	0/8	4/28	
No (n)	8/8	24/28	
I ¹³¹ therapy			1.000 *
Yes (n)	1/8	5/28	
No (n)	7/8	23/28	
Duration of exophthalmos (months)	60 (24 - 120)	6.5 (0 - 120)	0.001†
Subjective diplopia			0.301 *
Yes (n)	0/8	8/28	
No (n)	8/8	20/28	
LogMAR score	-0.040 (-0.176 - 1.301)	0.85 (-0.08 - 4)	0.004 †
Exophthalmometry (Hertel) (mm)	23.0 (21 - 28)	21.5 (15 - 27)	0.049 †
Keratopathy (n)			0.531 †
Absent	6/8	17/28	
Stippling of cornea	1/8	8/28	
Ulceration	1/8	2/28	
Clouding, necrosis, perforation	0/8	1/28	
Optic disc morphology (n)			0.395 *
Normal	6/7	15/25	
Edema	0/7	6/25	
Pale	1/7	4/25	
Clinical activity score	0.5 (0 - 3)	2 (0 - 5)	0.005 †
NOSPECS classification score‡	3 (3 - 6)	6 (4 - 6)	<0.001†
Dysthyroid optic neuropathy (n)			<0.001*
Absent	7/8	3/28	
Equivocal	0/8	3/28	
Definite	1/8	22/28	

Continuous variables are given as medians with ranges between the parentheses

* Fisher's exact test, † Mann-Whitney U Test

‡ NOSPECS classification score: score 0 = no signs and symptoms, score 1 = only signs, score 2 = soft tissue involvement, score 3 = proptosis, score 4 = extraocular muscle involvement, score 5 = corneal involvement, and score 6 = sight loss

into myofibroblasts and adipocytes^[14-16]. Additionally, Akaishi *et al's* study^[17] showed that TED patients with significant extraocular muscle enlargement had a higher frequency of the HLA-DRB1*16 allele, while patients without extraocular muscle enlargement had a higher frequency of the HLA-DRB1*03 allele. Their study suggests that these two subtypes of TED have different frequency of genetic markers, but this cannot explain why both subtypes simultaneously appeared in the same case. In the current study, one case had the predominant fat increase subtype in one eye and muscle increase subtype in the other, which has been identified as fat group for analysis. This phenomenon was also found in McKeag *et al's* study^[18].

Mechanistic explanations for DON differ between

the predominant fat increase and muscle increase subtypes^[19,20]. In the predominant fat increase subtype, the extraocular muscles without enlargement cannot limit the anterior movement of the globe (equal to self-decompression) caused by the fat volume increase. Moreover, a crowded orbital apex is not observed in this subtype. Rarely, exophthalmos is so severe that the optic nerve is stretched as a straight line, while the posterior globe is changed to a so-called "V" sign, leading to visual dysfunction (Fig 1)^[21]. In contrast, in the predominant muscle increase subtype, the optic nerve is compressed by the increased extraocular muscle, especially at the orbital apex (Fig 2)^[19]. In this study, for patients with the muscle increase subtype, 82% of patients with DON had visual acuities of 0.3

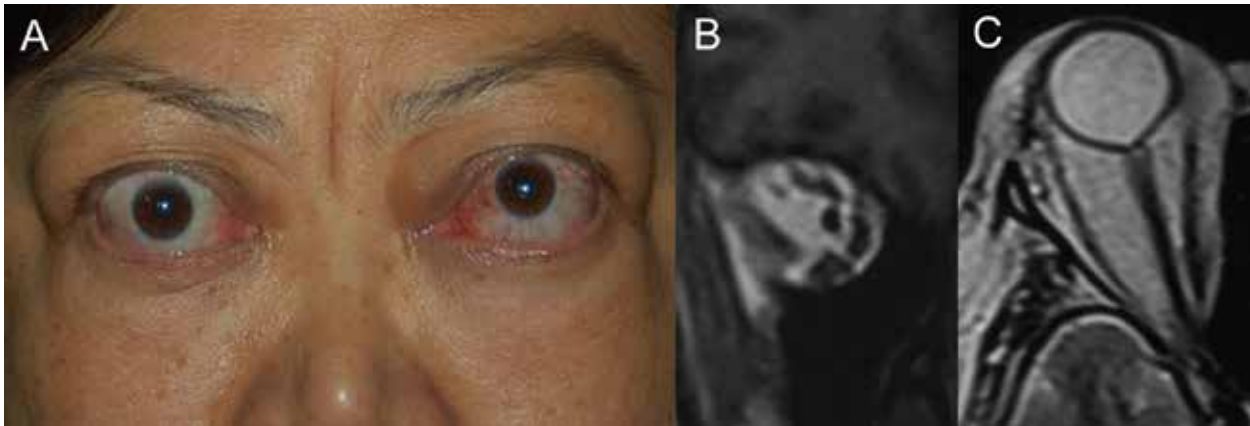


Fig 1: Dysthyroid optic neuropathy in the predominantly fat increase subtype of thyroid eye disease. (A) A 53-year-old woman had bilateral swelling and retraction of the eyelids, but keratopathy was not observed. Her corrected visual acuity was 0.4 in the right eye and light perception in the left eye. The coronal (B) and axial (C) magnetic resonance imaging views reveal that predominantly fat increased in her right orbit. Note that the right posterior globe was changed to a so-called “V” sign (C).

or poorer. Central scotoma is the most common (94%) visual field defect observed in DON caused by the enlarged extraocular muscles^[22], meanwhile, peripheral visual field defects seem always to be detected in DON caused by stretching^[23].

Although we did not identify a correlation between DON and gender, patients with the predominant muscle increase subtype tended to be older, compared to the predominant fat increase subtype. Wu *et al*^[24] and Chng *et al*^[25] found that older and male Chinese patients are more likely to be affected by DON. The probable reason for this association is that many male patients are cigarette smokers and that older patients usually had medical histories of diabetes, hyperlipemia, hypertension, and/or cardiac diseases. All of these variables are risk factors for varied optic neuropathies^[24,26-28], and might also contribute to a

higher percentage of DON in the predominant muscle increase subtype.

A major limitation in our study was that we only collected data from the hospitalized patients with relatively severe TED, although all patients undergo MRI as a routine examination. Patients with the predominant fat increase subtype, especially young women, were hesitant to agree to hospitalization because of concerns regarding the risk of disfigurement after surgery. Therefore, a few cases with the fat increase subtype could not be included in this study.

CONCLUSION

Our data from Chinese patients further support that distinct differences exist between the predominant fat increase and muscle increase subtypes. Although patients with the predominant fat increase subtype

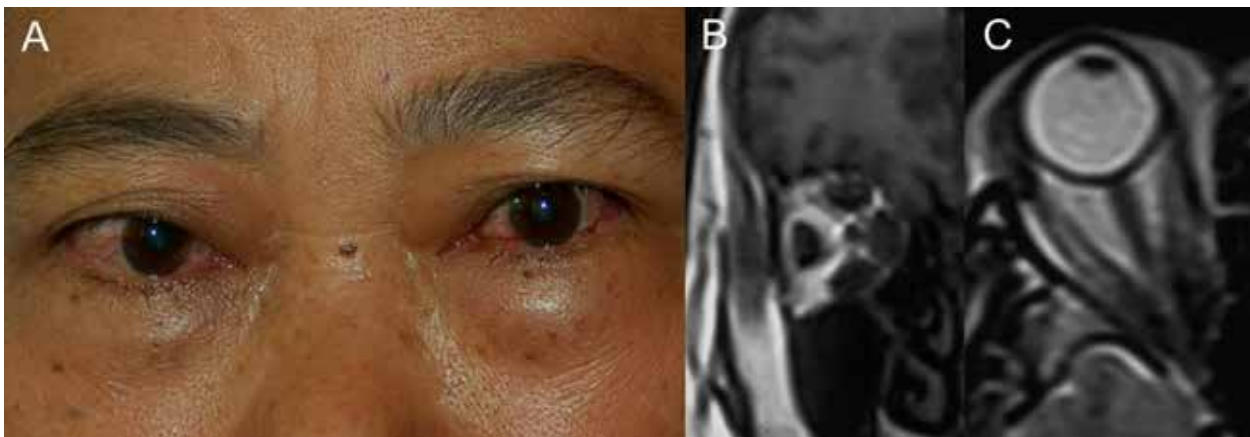


Fig 2: Dysthyroid optic neuropathy in the predominantly muscle increase subtype of thyroid eye disease. (A) A 51-year-old woman had bilateral swelling of the eyelids, congestion of the conjunctiva, and no keratopathy. Her corrected visual acuity was counting fingers in the right eye and 0.05 in the left eye. The coronal (B) and axial (C) magnetic resonance imaging views reveal significant enlargement of the extraocular muscles and a crowded orbital apex in the patient's right orbit.

experience a longer duration and higher degree of exophthalmos, these patients are much less susceptible to DON. Visual loss caused by DON in the predominant fat increase subtype was slight, likely because only the peripheral visual field was involved.

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Case Report

False Positive Positron Emission Tomography Study in Two Patients due to Microembolus of 18f-Fluorodeoxyglucose

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ABSTRACT

Oncology constitutes 75% of all clinical studies of positron emission tomography (PET). Glucose metabolism is increased in lung cancers like the other cancer cells. Integration of 18F-fluorodeoxyglucose (FDG) PET and computed tomography (CT) provides both anatomic and metabolic knowledge. PET-CT has an important role in lung cancer staging. Here, two cases of FDG microembolus were presented. Although there was an FDG uptake in PET-CT, it was not seen in CT images.

Case 1: Focal FDG uptake in right lower lobe. That lesion was regarded as FDG micro-embolus which appeared for

technical reasons because there was no lesion explaining that FDG uptake in CT.

Case 2: PET-CT showed a mass that is compatible with malignancy of high involvement in right lower lobe while focal FDG involvement that has no correspondence in correlated CT image was observed in the right upper lobe. It was evaluated that FDG focus belongs to FDG micro embolus caused by technical factors.

Microembolus may be one of the reasons of FDG uptake focuses which could not be proved tomographically. It may lead to some false positive interpretation.

KEY WORDS: cancer cells, computed tomography (CT), glucose metabolism, lung cancer

INTRODUCTION

Today, 2-(F-18)-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) has a permanent role in lung cancer staging. High sensitivity of FDG-PET reduces the need for additional procedures in diagnosis because it makes clear identification of the spread of the disease possible. However, it cannot give clinicians an anatomic reference to completely localize the focus of the disease. For this reason, PET and computer tomography (CT) devices have been introduced^[1,2]. The most important advantage of the combined systems is that they enable to correlate the lesions observed by PET CT with the morphological findings.

This study presents two cases that were considered as FDG micro-embolus. Lesions could not be shown on CT images, although they were evident on FDG-PET images.

CASE REPORT

Case 1

A 53-year-old male patient came to our clinic with the complaint of hemoptysis. Physical examination and routine laboratory examination were normal. In thorax computerized tomography, soft tissue mass causing congestion in right upper lob- bronchus of hilar region in right lung and in branches of adjacent bronchus, and calcified granuloma in right lung, and sequel changes in both lung apices were noted. In fiber optic bronchoscopy, endo-bronchial mass lesion obstructing the entry of right upper lobe was observed and it was evaluated as carcinoma with squamous epithelium cell. High involvement of the mass was observed in the right upper lobe and focal FDG involvement that has no correspondence in correlated CT image was observed in the right lower lobe (Fig 1). Upper lobectomy was performed on the patient and no

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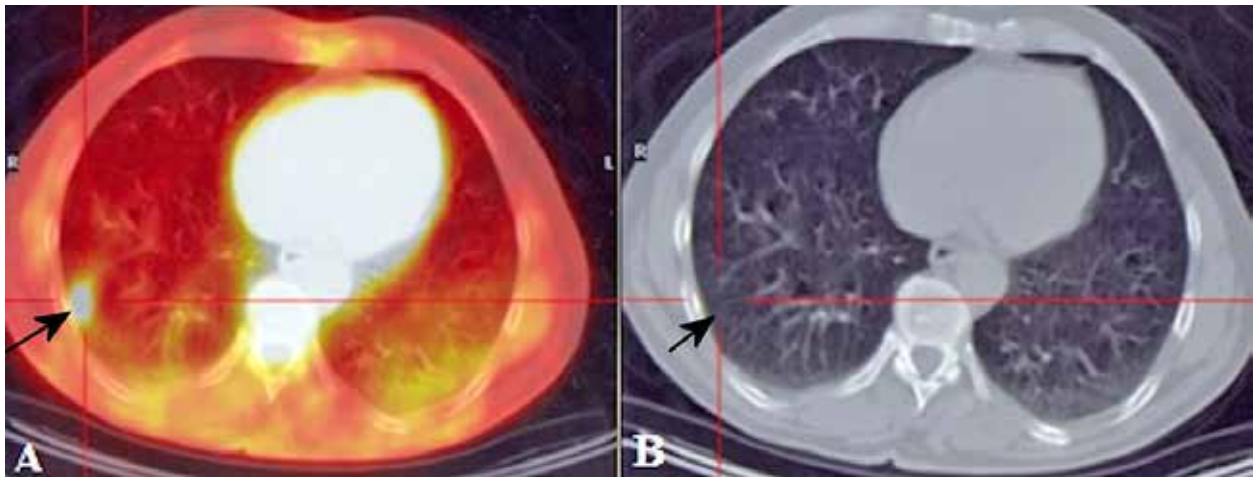


Fig 1: (a) PET-CT image showing focal FDG involvement in the right lower lobe (b) Correlated CT image showing normal right lower lobe

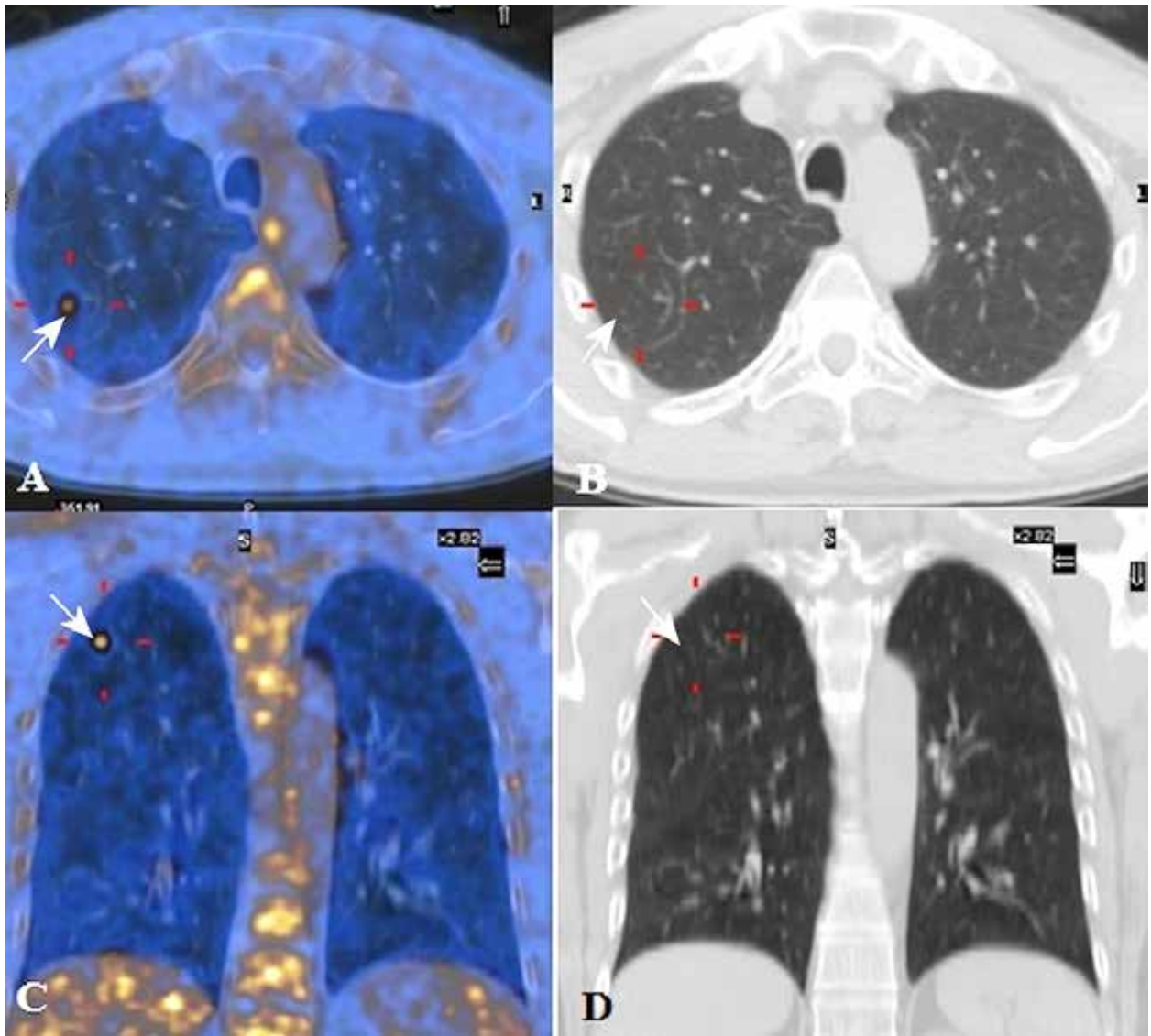


Fig 2: (a,c) PET-CT images showing focal FDG involvement in the right upper lobe (b,d) Correlated CT image showing normal right upper lobe

lesions were identified in the region which had been considered to have FDG micro embolus in lower lobe during operation. At 12-month follow up, relapse or metastases was not identified in the patient.

CASE 2

A 58-year-old male patient admitted to our clinic with the complaint of chest pain. Physical examination and routine laboratory examinations were normal. In thorax computerized tomography, soft tissue mass that is adjacent to thorax wall was identified in lower lobe. In fiberoptic bronchoscopy, endobronchial lesion was not observed. Transthoracic fine needle aspiration biopsy was performed on the mass. In consequence of pathological examination, it was evaluated as carcinoma with squamous epithelium cell. In PET-CT, malignant characterized mass with high involvement was observed in right lower lobe while focal FDG involvement that has no correspondence in correlated CT image was observed in the right upper lobe (Fig 2). It was evaluated that focal FDG focus belongs to FDG micro embolus caused by technical factors. Lower lobectomy was performed on the patient and lesion was not identified in upper lobe during operation. At the 20-month follow-up, there were no lesions identified.

DISCUSSION

Various inflammatory and benign diseases were mimicking local or far tumors on PET-CT by having FDG at a considerable level^[3,4]. However, PET-CT has become a standard imaging tool for primer staging and evaluation of the response to treatment in oncologic patients. It is also used in 75% of oncologic studies^[5].

In the study of Jung Min Ha *et al*, accidental FDG involvement that has no anatomic correspondence in CT was identified. After 1 - 3 days, recurrent PET-CT was performed to the patient and it was observed that there was no abnormal uptake in the same region^[6]. During FDG injection, micro embolus was formed by intravenous injection procedure (first aspirate to check the syringe in the vein and re-inject aspirated blood). It was considered to be related to the congestion in capillary vein of lung^[7,8]. Under these conditions, energy needs increase depending on the increase of GLUT-3 level at active platelets. In the studies, it was observed that glucose uptake had increased in these cells under invivo conditions^[9]. Increased glucose uptake caused FDG involvement and misleading images in PET-CT. In these types of cases, FDG uptake of PET-CT after 30 min was detected more in peripheral region. This technique helps differentiate

the artifacts from real lesions^[6]. There is no need for another PET-CT because lesion was not observed in thin section thorax tomography in these cases. The inability to identify lesions in the regions thought to have FDG micro embolus during surgery also helped justify the diagnosis.

CONCLUSION

FDG injections require more attention and blood withdrawal to the syringe should be avoided. Possible micro embolus should also be considered when there is pulmonary FDG focal uptake without corresponding abnormality on CT. This should be kept in mind as a cause of false positive result in tumor staging.

ACKNOWLEDGMENT

Declaration: No conflict of interest

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Case Report

Ineffectiveness of Low-Dosage Idebenone on Chinese Patients with Leber's Hereditary Optic Neuropathy: Report of Two Cases

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ABSTRACT

The present study reports that the low-dosage idebenone on Chinese patients with Leber's hereditary optic neuropathy (LHON) is likely to be ineffective.

In case 1, an 18-year-old Chinese male had sequentially painless blurring of bilateral eye for two months. Genetic testing revealed that the LHON 11778 was positive. He was subsequently put on oral idebenone 30 mg three times daily. Two months later, the dosage of idebenone increased from 30 mg to 90 mg three times daily due to ineffective treatment. During a 17-month follow-up, his best corrected visual acuity

was still not elevated.

In case 2, a 22-year-old Chinese male presented to us with a history of progressive painless blurring of vision in the bilateral eye for five months. Genetic testing revealed that the LHON 11778 was positive. He was then put on oral idebenone 150 mg three times daily. During a 13-month follow-up, his best corrected visual acuity was still not improved. Therefore, the dosage of idebenone, less than 450 mg/day, on Chinese patients with Leber's hereditary optic neuropathy is probably ineffective.

KEY WORDS: genetic testing, mitochondrial complex III, mtDNA, optic atrophy, side effects**INTRODUCTION**

Leber's hereditary optic neuropathy (LHON) was first described by the German ophthalmologist Theodore Leber in 1871 as a maternally inherited disease characterized by bilateral, usually sequential, acute or subacute visual loss^[1]. The minimum prevalence has been estimated at 1 in 31,000 in the North of the United Kingdom. Comparable prevalence figures of 1 in 39,000 and 1 in 50,000 have been reported in epidemiological studies from the Netherlands and Finland, respectively^[2]. The peak age of onset in LHON is between the ages of 15 – 30 years and 95% of carriers who will experience visual failure will do so before the age of 50^[1]. Diagnosis is by identification of one of the three mtDNA point mutations: 11778, 3460 and 14484. So far, there are few therapeutic options for patients currently. According to a review of recent reports, certain case reports have demonstrated that idebenone was probably efficacious in the early-stage

for LHON patients with vision loss, and may help to shorten the interval of visual recovery^[3]. However, the majority of the case reports on LHON treated with idebenone were reported in Europe. It is very rare for Chinese patients to have undergone treatment with idebenone.

CASE REPORT**Case 1**

In January 2015, an 18-year-old Chinese male was referred to the Department of Ophthalmology, First Affiliated Hospital of Guangxi Medical University. He had progressive, painless blurring of bilateral eye for two months before he presented at our clinic. Two months ago, he was diagnosed with retrobulbar optic neuritis at local clinics and received treatment of corticosteroid pulse therapy without improvement in vision. There was no family history of ocular diseases or ocular trauma.

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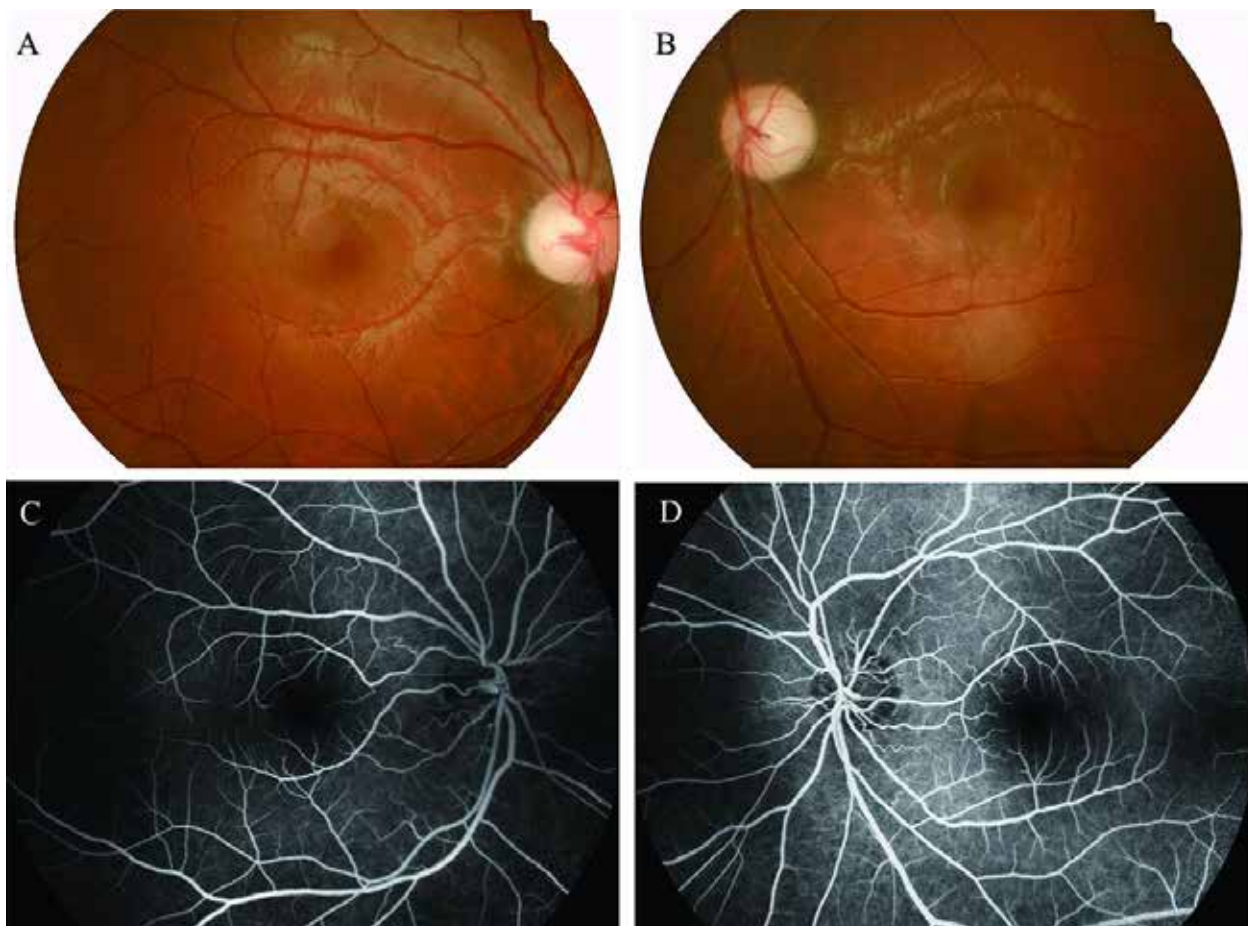


Fig 1: In case 1, an 18-year-old Chinese male with confirmed LHON. Atrophy of bilateral optic nerves (A: right eye; B: left eye). There was no leak from the optic disk (C: right eye; D: left eye) during fluorescein angiography.

On examination at our clinic, his best corrected visual acuity was 0.03 and counting fingers at 20 cm in the right and left eye, respectively. The left eye showed relative afferent papillary defect. Both of the optic nerves were atrophic without peripapillary hemorrhage or swelling on ophthalmoscopic examination (Fig 1). There was no leak from the optic disk and arterioles during fluorescein angiography (Fig 1). Optic coherence tomography revealed that bilateral nerve fiber layers and ganglion cell layers were thin; meanwhile, optic disk cup was enlarged. Blood test, liver function test and renal function test were not special. Magnetic resonance imaging (MRI) of the brain was unremarkable at another hospital.

We then submitted the blood sample that was collected from the patient in our hospital to genetic laboratory of Zhongshan Ophthalmic Center for analysis. Genetic testing revealed that the 11778 was positive.

Since the monolithic dosage of idebenone made in Chinese pharmaceutical factory is very low (30 mg per tablet), after obtaining the patient's agreement,

he was then put on oral idebenone 30 mg three times daily and oral vitamin C 100 mg three times daily. Two months later, the dosage of idebenone was increased from 30 mg to 90 mg three times daily due to ineffective treatment. He was advised not to smoke and to avoid high alcohol consumption. During a 17-month follow-up, his best corrected visual acuity was still not elevated.

At the fourth month after taking the idebenone, he started to appear nystagmus. There were no other significant treatment-related side effects.

Case 2

A 22-year-old Chinese male presented to us in April 2015 with a history of progressive, painless blurring of vision in the bilateral eye for five months. Five months before he presented at our clinic, he was diagnosed with myopia at local clinics. The treatment was unclear and the symptoms aggravated gradually. The patient was referred to ophthalmology department of Liuzhou People's Hospital in April 2015. He was diagnosed with retrobulbar optic neuritis. He received treatment

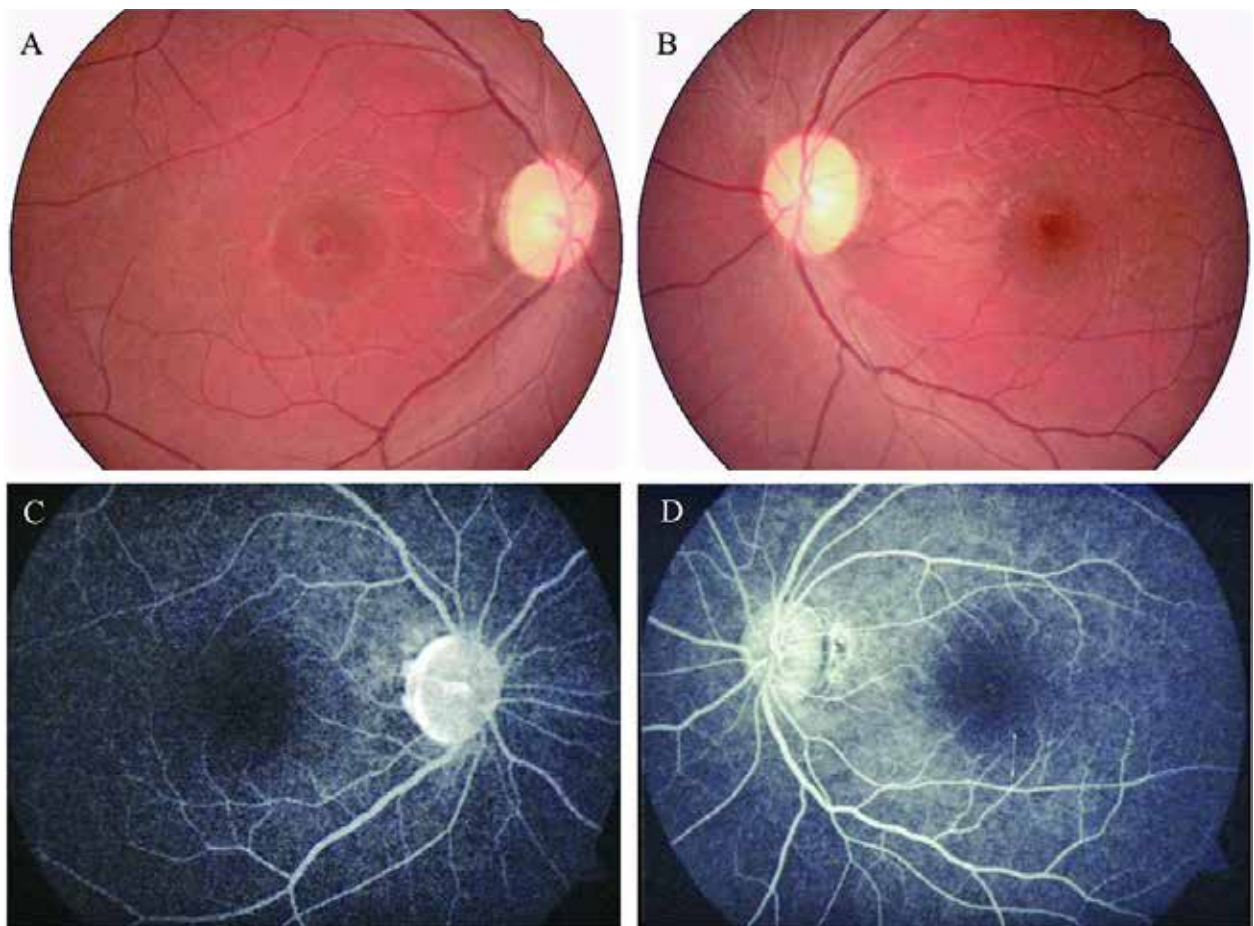


Fig 2: In case 2, a 22-year-old Chinese male with confirmed LHON. Atrophy of bilateral optic nerves (A: right eye; B: left eye). Fluorescein angiography of the bilateral eye (C: right eye; D: left eye) reveals hypo-fluorescence of optic disk.

of corticosteroid pulse therapy and oral citicoline 0.2 g three times daily and ginkgo biloba leaves extract tablets 19.2 mg two times daily. However, his visual function was not improved. He had a history of alcohol consumption. The family history of ocular diseases and ocular trauma were not special.

On examination at our clinic, his best corrected visual acuity was 0.05 in the right eye and 0.04 in the left eye. The findings on slit-lamp examination were unremarkable in both eyes. Bilateral of optic nerves were atrophic without peripapillary hemorrhage or swelling on ophthalmoscopic examination (Fig 2). Visual evoked potential revealed prolonged P100 latency. Visual field testing by perimetry showed diffuse loss in both eyes. Optic coherence tomography revealed that bilateral nerve fiber layers were thin. The image of fluorescein angiography displayed hypo-fluorescence in bilateral optic disk (Fig 2). Blood test and blood glucose were normal. Liver function test and renal function test were not special. MRI of the brain and orbit was unremarkable.

We then submitted the blood sample that was collected from the patient in our hospital to the genetic laboratory of Zhongshan Ophthalmic Center for analysis. Genetic testing revealed that the 11778 was positive.

He was subsequently put on oral idebenone 150 mg three times daily. Meanwhile, he was advised not to smoke and to avoid high alcohol consumption. During a 13-month follow-up, his best corrected visual acuity was still not improved.

After taking the idebenone, the drug gave an edge to patient's appetite immediately and the weight was increased from 55 kg to 65 kg. When the drug usage was stopped, patient's appetite returned to normal, but the weight maintained at 65 kg. There were no other significant treatment-related side effects.

DISCUSSION

LHON is an inherited disorder characterized by bilateral progressive and debilitating vision loss without generally accepted measures^[1,2]. Over 95%

of affected families are now known to harbor one of three mtDNA point mutations: 11778, 3460 and 14484, which all involve genes encoding complex I subunits of the mitochondrial respiratory chain^[1]. As a result, mitochondrial ATP generation is decreased and the oxygen-free radicals are added, leading to apoptosis of retinal ganglion cells. Idebenone is a short-chain benzoquinone as coenzyme Q10^[4,5]. The mechanism of idebenone is potent antioxidant capacity and acts as a mitochondrial electron carrier, thereby restoring cellular energy (ATP) production by transferring electrons directly to mitochondrial complex III^[4].

From a pharmacological point of view, the idebenone is an anti-oxidant thought to help restore mitochondrial function and prevent oxidative damage in retinal ganglion cells in LHON patients^[6], but there is no research showing that the idebenone can repair or regenerate the retinal ganglion cells which has been apoptosis. Therefore, the visions of patients treated with idebenone were probably not significantly increased. Klopstock conducted a 24-week, multi-center, double-blind, randomized, placebo-controlled trial in 85 patients with LHON^[7]. For the best recovery of visual acuity measured by logMAR, the difference between the placebo group and the idebenone group (900 mg/day) did not reach statistical significance at 24 weeks. In our cases, the visions of patients with LHON who were treated with low-dosage idebenone were also not remarkable. However, it should be noted that although vision improvement is not obvious, idebenone can protect from loss of color vision^[7,8] and prevent progression of LHON.

There was a wide range of administrative dosages of oral idebenone (90 - 900mg/day)^[4,7,9]. Recently, idebenone 150 mg tablets (Raxone® Or Catena®) was used as a disease-specific treatment for LHON in Europe^[4,6,7]. However, in China, monolithic dosage of idebenone made in Chinese pharmaceutical factory is very low (30 mg per tablet) and the pharmaceutical instruction recommends 30 mg three times daily. In case one, the recommended dosage (30 mg per tablet) was not effective. What is more, when the dosage of idebenone increased to 270 mg/day in case one and 450 mg/day in case two, respectively; their best corrected visual acuity was still not elevated. There is currently no evidence showing that the idebenone has racial and ethnic differences in responses. Currently, Cheng SW administered idebenone, which came from overseas, to a patient with LHON at 900 mg/day in Hong Kong, China^[3]. The bilateral visual acuity had improved in various degrees. Therefore, further work is needed to confirm if the drug processing technology and drug potency are different between

idebenone 150 mg tablets (Raxone® Or Catena®) and the drug made in Chinese pharmaceutical factory. In addition, in the future we may increase the dosage of idebenone, such as 900mg/day, to observe the therapeutic effect in Chinese patients.

The dosage of idebenone was well tolerated and safe. The most common side effects are nasopharyngitis, cough, diarrhea and back pain^[6]. In our cases, the patient appeared nystagmus and weight gain, respectively; to our best knowledge, there was currently no related studies reporting those side effects.

CONCLUSION

The main objective of this report was to demonstrate that the dosage of idebenone, less than 450 mg/day, on Chinese patients with LHON is probably ineffective. To our knowledge, this is the first study to treat patients with LHON in Chinese mainland with idebenone. It adds a new dimension to our understanding of the therapeutic dosage of idebenone, and offers a starting point to confirm the therapeutic dosage of idebenone on Chinese patients. Of course, greater sample sizes and a longer follow-up period are required to fully determine the viewpoint in the future. In addition, we still need to pay attention to the side effects of idebenone, such as nystagmus and weight gain.

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Case Report

Thromboembolism (TE) Events as First Presentation of Ulcerative Colitis (UC)

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ABSTRACT

Inflammatory bowel disease (IBD) is a multisystem disorder that primarily affects the gastrointestinal tract. Patients with IBD have increased chance of developing thromboembolism (TE) events, which is a significant

cause of morbidity and mortality. This report describes a case of two TE events, cerebral arterial thrombosis and pulmonary embolism, as a first manifestation of ulcerative colitis.

KEY WORDS: cerebral artery thrombosis, inflammatory bowel disease, pulmonary embolism

INTRODUCTION

Inflammatory bowel disease (IBD) is a multisystem disorder that primarily affects the gastrointestinal tract characterized by inflammation and ulcerations of the bowel. The IBD is categorized into ulcerative colitis (UC) and Crohn's disease (CD)^[1]. The prevalence of IBD worldwide is reaching up to 396/100,000 persons and it has been noted to be more common in South East Asian populations^[2]. In both IBD types, gastrointestinal and extra-intestinal manifestations occur. The extra-intestinal manifestations include arterial and venous thrombosis^[3]. Studies indicate increased risk of patient with UC to develop arterial and venous thrombosis when compared to the general population. Most patients with IBD develop venous thromboembolism (VTE) in the pulmonary system and the deep veins of the legs^[4]. Thromboembolism (TE) events including the pulmonary embolism (PE), deep venous thrombosis of the lower limb (DVT) and the superior sagittal sinus thrombosis (SSST) are predominantly serious cases that are closely associated with increased mortality. The patients also have increased possibility of developing VTE in the mesenteric and portal veins. However, VTE can also be developed in other parts including the retinal and cerebrovascular veins. Over the past decade, increased cases of VTE reported have been closely

associated with IBD^[1]. The high risks of developing TE events from IBD have been observed in both hospital-based and population-based epidemiological studies. Besides, the studies of hospitalized patients have also observed increased mortality associated with VTE within ulcerative colitis^[5]. Here, we describe a case of stroke due to arterial thrombosis as a first presentation of ulcerative colitis, followed by pulmonary embolism two week later, despite being on prophylactic anticoagulants.

CASE REPORT

A 48-year-old South-East Asian presented to the emergency department with sudden onset of left-sided hemiparesis associated with numbness and headache. The patient is not known to have any medical disease other than well-controlled type II diabetes mellitus on metformin. He is a non-smoker with no family history of atherosclerotic disease. On examination, patient was conscious, oriented in time, place and person. He was afebrile and normotensive. Cardiovascular, respiratory and abdominal examinations were unremarkable. Central nervous system examination revealed left sided upper motor neuron facial palsy with left sided weakness (power 3/5). Laboratory investigations showed normal complete blood count,

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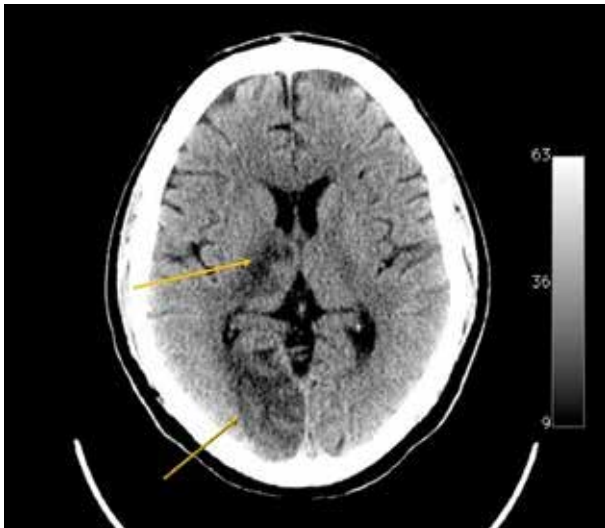


Fig 1: Computed tomography (CT) brain showed an acute middle cerebral artery thrombosis involving right thalamus and right internal capsule. In addition, acute thrombosis along right posterior cerebral artery was also noted involving occipital lobe and to lesser extent temporal and parietal lobes.

erythrocytes sedimentation rate (ESR), C-reactive protein (CRP) and renal function test. He had normal sinus rhythm in the electrocardiogram study. The patient was shifted urgently to radiology department and computed tomography CT brain (Fig 1) showed an acute middle cerebral artery thrombosis involving right thalamus and right internal capsule. In addition, acute thrombosis along right posterior cerebral artery was also noted involving occipital lobe, and to lesser extent, temporal and parietal lobes. Later carotid Doppler and echocardiography were done and both were normal. The patient was admitted to the medical ward and anti-platelets agent was initiated. Physiotherapy and prophylactic low molecular weight heparin (LMWH) (Enoxaparin) were started in succession.

After two weeks of hospitalization, the patient developed sudden onset of pleuretic chest pain, shortness of breath and tachycardia. Chest computed tomography angiography (Fig 2) was done urgently

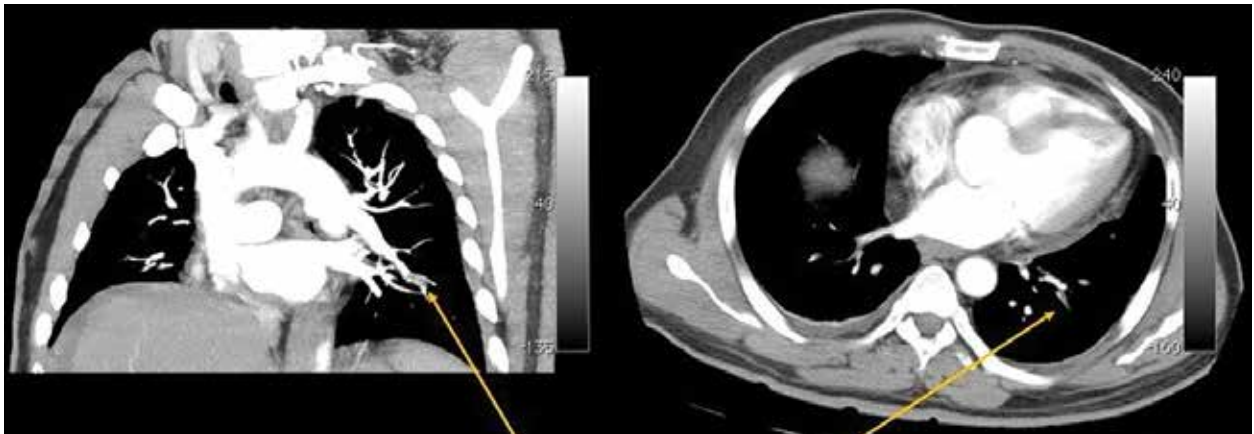


Fig 2: Chest computed tomography angiography of patient showed left lateral basal segment embolism (both arrows).

Colonic Ulcer

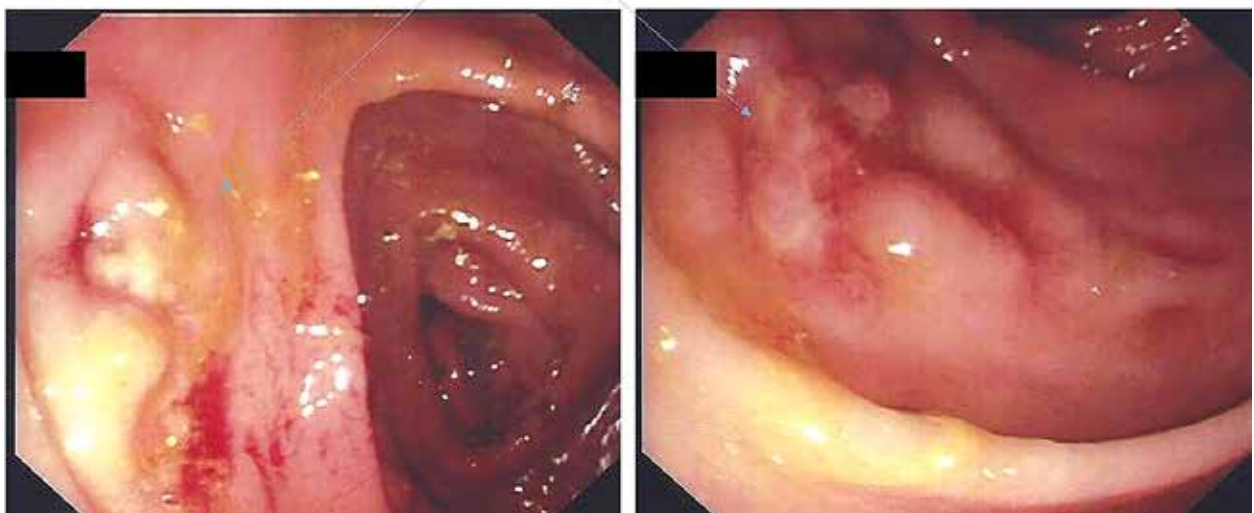


Fig 3: Abdominal X-ray of patient shows multiple air fluid levels

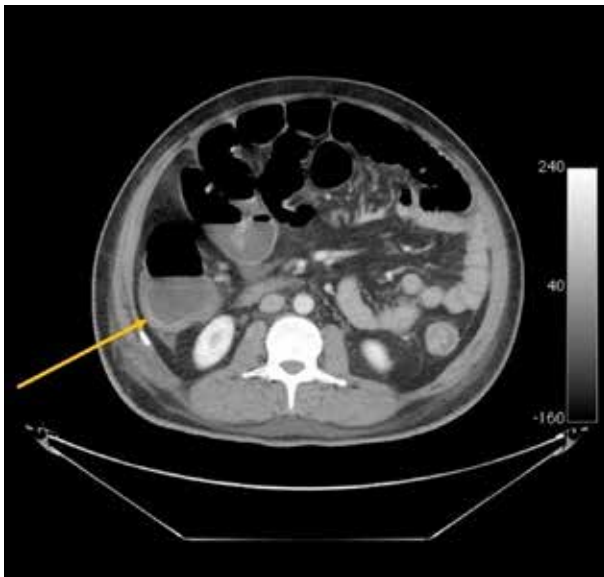


Fig 4: Abdomen computed tomography of patient showed colonic wall thickening suggestive of colitis

and showed left lateral basal segment embolism. Hence, the patient was switched to therapeutic doses of LMWH.

At this stage, all studies for thrombophilia were negative, including protein S, protein C, antithrombin III, and factor V Leiden. Connective tissue disease markers such as anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), anticardiolipin and lupus anticoagulant antibodies were negative. Venereal disease research laboratory (VDRL) and cryoglobulins were negative. Furthermore, one week later, the patient developed severe colicky abdominal pain associated with vomiting and constipation suggestive of an acute abdomen. Abdominal X-ray (Fig 3) showed multiple air fluid levels and abdominal CT angiogram (Fig 4) revealed circumferential wall thickening involving the entire colon with mild to moderate degree of obstruction, suggestive of inflammatory bowel disease with no evidence of ischemic colitis. The patient was managed conservatively and thereafter a colonoscopy (Fig 5) was performed. It showed active pancolitis with ileo-caecalvalve incompetence and back wash ileitis. Several colonic biopsies were obtained and reported architectural distortion with crypt budding and branching associated with increased inflammatory cells in the lamina propria, focal active inflammation of surface epithelium and no granuloma identified giving a diagnosis of ulcerative colitis. Treatment with oral mesalazine was initiated and significant improvement was noticed. The patient was discharged on anticoagulation for the pulmonary embolism (PE),



Fig 5: Colonoscopy views of patient showed ulceration compatible with ulcerative colitis

immunosuppressant for the UC and physiotherapy for the residual limb weakness.

DISCUSSION

The incidence of venous thromboembolism in IBD patients ranges from 1.3% - 8% with necroscopic studies estimating it to be around 40%^[6]. Studies also indicate no significant difference in the risk of VTE between CD and UC patients. The mortality rates among the IBD patients with VTE are estimated to be between 8% and 25%^[6]. Besides, the occurrence of thromboembolic events is more common among IBD patients below 50 years of age and is more prevalent among women compared with men^[7]. However, recent studies indicate that the risks of thromboembolic events (TE) are prevalent in men compared with women^[4]. Evidence indicates that IBD is an independent risk factor for thromboembolism^[3]. Studies also indicate that pregnant IBD women have increased risk of developing TE compared with non-IBD obstetric population^[8]. Most of the thromboembolism events ensue all through active disease even though high rates of thrombosis are testified during diminutions and well-controlled disease^[4]. Incidences of TE have also been found to correlate with the magnitude of the disease such as the pan-colonic envelopment in ulcerative colitis and colonic connection with CD^[5].

Many factors have been linked to the tendency of thromboembolism, including genetic and non-genetic factors. However, the exact mechanism behind this phenomenon is still not completely understood. Diverse mechanisms have been hypothesized for thrombosis in ulcerative colitis such as hyper-coagulation, abnormalities of the platelets, endothelial dysfunction and immunological abnormalities. Hyper coagulation is manifested in the fibrinogen, decrease in the antithrombin, protein S and protein C, hypo-fibrinolysis including elevated PAI-1 and lipoprotein (a).

However, unique causes have not been established. Factor V Leiden mutation, inherited hyperhomocysteinemia and prothrombin gene mutation, Gene polymorphism, deficiency of protein C and S, and antithrombin III mutation, which are genetic causes of thrombophilia are not significantly associated with IBD and do not explain the increased TE risk in CD and UC patients^[4]. Patients who are diagnosed with VTE are recommended for the work up in order to determine the underlying causes^[9]. Rectal examination, fecal occult blood testing and colonoscopy are often recommended for the first step diagnosis to rule out malignancy, which is a strong risk factor for VTE^[9]. In situations where inherited causes are absent, acquired causes play a critical role. However, most of these acquired causes including smoking, immobilizations, fluid depletion and hormonal therapy were absent in the patient.

The current guidelines on how to treat venous thromboembolism (VTE) does not include patients with IBD, yet this presents the group with high risk of gastrointestinal bleeding and VTE. Substantial data indicate that IBD is a risk factor for VTE. Even though gastroenterological surveys indicate increased recognition of this risk by physicians, uncertainty still remains regarding the management of VTE among IBD patients, such as the application of prophylaxis among the inpatients with non-IBD conditions^[10]. Even though the guidelines are absent, a consensus has been reached on the manner in which VTE can be managed among the IBD patients indicating VTE patients. The consensus built among the multidisciplinary group recommends that prophylaxis should be applied and anticoagulant is preferable to the mechanical prophylaxis for in-patients with mild or severe prolonged IBD hospitalization indicating increased chances of VTE^[8]. Heparin application has not been fully proved to be effective in therapeutic management, even though it has been recommended based on limited evidence. However, thrombolytic agents have proved to be a lifesaver for the IBD patients with severe VTE^[4].

IBD patients with increased risk of developing VTE, particularly hospitalized patients, are supposed to be on the prophylactic anticoagulant. Besides, unfractionated heparin (UH) and low molecular-weight heparin (LMWH) are supposed to be used for thromboprophylaxis in IBD patients^[10]. However, randomized controlled trials that have examined the anticoagulant effectiveness for VTE prophylaxis in IBD patients are lacking. Most of the controlled trials have focused on the effects of pharmacological prophylaxis on severely ill patients and have demonstrated that pharmacological prophylaxis has considerably eased the risks of VTE among the hospitalized patients^[11,12]. Considering the above complications, multidisciplinary approach is recommended for the treatment and management of these patients. The current consensus recommends that IBD patients with VTE do not need to test for the hereditary or acquired hypercoagulability states^[10]. Under the conditions that any aggravating aspect in clinical lessening state of IBD patient is lacking, then at least three months of anticoagulant therapy is recommended^[4]. However, this is subject to periodic re-evaluation. The pulmonary computed tomography, angiography and echocardiography is unanimously recommended for re-evaluation of the anticoagulant therapy. It should be noted that there is no difference between managing acutely TE event in patients with IBD and others. However, electrocardiography and echocardiography are unanimously agreed to be applied for patients diagnosed with pulmonary thromboembolism. Our call for discussion pivots on two major issues: one being whether we should consider screening patients with thromboembolic events for IBD. The second point is if we should take special considerations for prophylactic anticoagulants to protect against TE events.

CONCLUSION

Patients with IBD have increased chance of developing TE, which is a significant cause of morbidity and mortality. Most patients with IBD develop TE in the pulmonary system and the deep veins of the legs. IBD has remained a single risk factor of VTE. Even though gastroenterological surveys indicate increased recognition of this risk by physicians, uncertainty still remains regarding the management of TE among IBD patients and further efforts are required to establish guidelines in the management of TE in UC. Whether to consider screening patients with thromboembolism events for IBD to be able to prevent future complications that may be developed during the treatment process is a considering point.

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Conflict of Interest: The authors declare no conflicts of interest.

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Case Report

A Small Cell Carcinoma of the Breast

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ABSTRACT

Primary small cell neuroendocrine carcinoma of the breast is a rare disease. It was originally described in the breast in 1963 but appeared in the World Health Organization classification of the breast in 2003. We report a case of a

42-year old woman with locally advanced disease where neoadjuvant chemotherapy did not have any effect and mastectomy with axillary dissection and transverse rectus abdominis myocutaneous flap was done.

KEY WORDS: breast cancer, mastectomy, neuroendocrine

INTRODUCTION

Primary neuro endocrine carcinoma (NEC) of the breast was originally described in the breast cancers with carcinoid-like growth patterns in 1963^[1]. However, the formal criteria for mammary NEC were not established until 2003, when the World Health Organization (WHO) classified the interpretation of the phenomenon of neuroendocrine differentiation in breast cancer as having more than 50% neoplastic cells expressing neuroendocrine markers^[2]. The WHO estimates that this uncommon and under-studied malignancy represents approximately 2 - 5% of breast carcinomas^[2]. The morphologic features of primary NEC of the breast are similar to those of neuroendocrine tumours of the lung and gastrointestinal tract, and the diagnosis can be performed if non-mammary sites are excluded or if an insitu component can be found^[3]. It comprises carcinoid tumours, large cell neuroendocrine carcinomas and small cell carcinoma^[4]. The tumor is primarily a disease of the middle aged (median age 55 years with a range of 41 - 70 years) and is predominately managed as other breast carcinomas - with surgery and adjuvant chemotherapy and/or radiation^[5]. Small cell neuroendocrine carcinoma (SCNEC) has been described in many extra-pulmonary sites including breast, larynx, gastrointestinal tract, prostate, bladder, ovary and cervix^[6]. We present a rare

case of a locally advanced small cell carcinoma of the breast in a middle-aged female discussing the possible management of such a case.

CASE REPORT

A 42-year-old Filipino lady, previously healthy, presented to the surgical out-patient clinic on May 2016 complaining of a painful lump in her left breast. The lump was noticeable for 4 months and was increasing in size with skin changes. The patient was still menstruating and had given birth to 3 children. There was no family history of breast or ovarian cancers, no history of oral contraceptive use and no history of weight loss. On examination, there was a bulging hard mass 5x5 cm in the upper outer quadrant at 1 - 2 O'clock of the left breast associated with scattered small skin nodules and areas of skin inflammation and hardness with nipple retraction and palpable left axillary lymph nodes (Fig 1). The right breast and axilla were normal. There was no supraclavicular lymphadenopathy, no jaundice and the chest with the abdominal examination were unremarkable. A combined mammography with ultrasonography of the breast was performed and revealed the lesion as BIRADS-5 (Fig 2). The laboratory investigations including tumour markers were within normal ranges. Histopathological examination of the core biopsy showed neuroendocrine carcinoma,

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Fig 1: A photograph of the lesion

poorly differentiated (small cell carcinoma) with negativity for ER, PR, HER-2 neu and chromogranin. The Ki-67 proliferative index was 100% and a focal positivity for CK7, CD56 (Fig 3 A&B). Following the diagnosis, the patient underwent a computerized tomography (CT) of the chest, abdomen and pelvis along with positron emission tomography (PET) scan in order to search for metastasis as well as to identify an occult extra-mammary primary carcinoma. The scan revealed no evidence of other primary lesion but metastasis to the liver and bone were positive (Fig 4). The patient was staged as a locally advanced and metastatic breast cancer and was considered a candidate for neoadjuvant chemotherapy. After 3 cycles of chemotherapy in the form of Adriamycin, Flurouracil and Cyclophosphamide, the tumour did not show any significant changes in the size or the skin involvement. The case was discussed with the

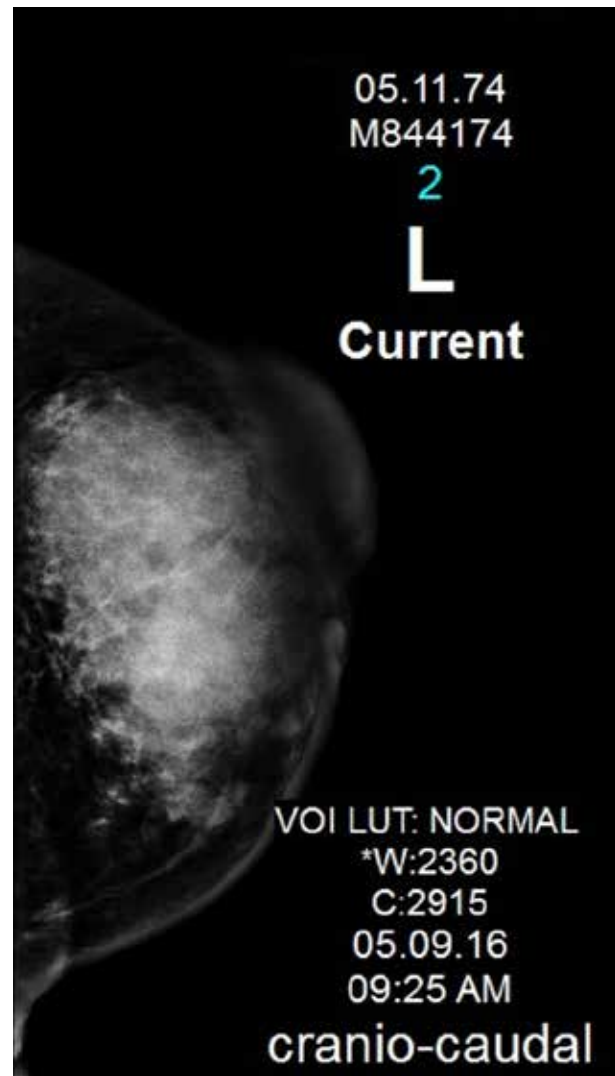


Fig 2: A mammography showing the mass

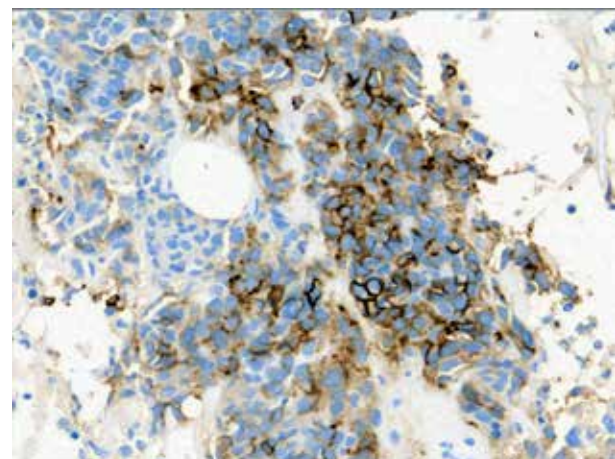
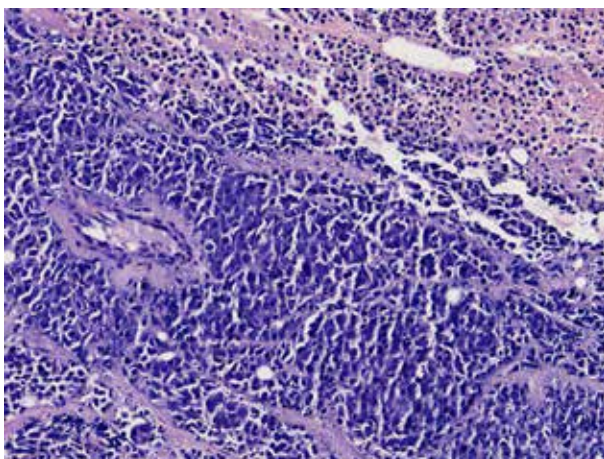


Fig 3 A&B: Slide pictures showing histopathological features of the disease

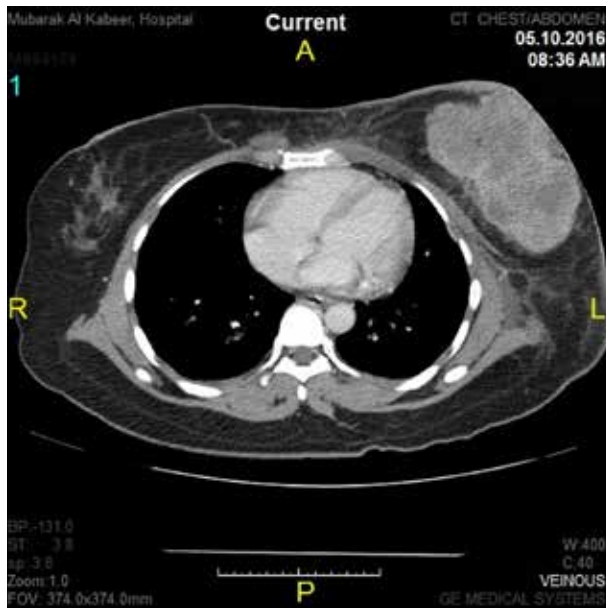


Fig 4: A CT scan showing the lesion

patient and she agreed for surgery. A modified radical mastectomy with axillary dissection and a transverse rectus abdominis myocutaneous flap was done to cover the area as most of the breast skin was excised. The patient tolerated the procedure well and was discharged for a regular follow-up in the out-patient.

DISCUSSION

Primary NEC of the breast is rare. These tumours are usually primary in the lungs and are highly malignant with very poor prognosis^[4]. However, metastatic neuroendocrine tumours to the breast have also been reported^[7]. The tumours of the breast other than ductal, lobular, and ductal to lobular types are called “rare breast cancers” and compromise 8 - 9% of all breast cancers^[8]. Small cell breast cancer is probably the least frequent one among rare breast cancers^[9]. Most of these cases are found in women, as is the case with breast carcinomas of the usual type. Only one case occurring in a 52-year-old man has been reported in the literature^[10]. The histogenesis of these tumours are still unclear because the presence of neuroendocrine cells in normal breast has not been proven conclusively^[11]. It has also been suggested that SCNEC is a variant of metaplastic carcinoma arising from usual lobular or ductal carcinoma^[12]. However, other reports believe that SCNEC is a distinct type of breast carcinoma different from the usual types of carcinoma, with variable degree of neuroendocrine differentiation and carrying worse prognosis^[6]. The histological appearances of these tumours in all sites are similar. Reports also suggest that the clinical

course of extra-pulmonary SCNEC is as aggressive as it's pulmonary counterpart^[6]. In order to give the diagnosis of primary small cell carcinoma of the breast, there should be no focus other than the breast or insitu component should be displayed. The insitu component has been reported in 2/3 of the patients reported in literature. Screening of other parts of the body is more important for the cases with no insitu component^[6]. Small cell breast cancers are high grade tumours with increased lymphovascular invasion and mostly with negative hormone receptors and therefore they have low survival rates, but with the increased number of cases reported in the literature, the survival has been shown to be related to the stage of the disease at the time of diagnosis^[13]. The standard therapy for this rare tumour remains controversial. Treatment is limited to surgery, such as mastectomy or lumpectomy, with axillary node dissection^[14]. Despite the similarities between pulmonary small cell carcinoma and extra-pulmonary small cell carcinoma in terms of presentation, prognosis, and natural history, few of these cancers are managed with combination chemotherapy and radiation therapy, which is the standard of care in pulmonary small cell carcinoma^[5]. In addition to chemotherapy and radiation, hormonal therapy has also not demonstrated an advantage in overall survival in comparison to ductal carcinoma^[15]. Most patients are treated the same way as for adenocarcinoma of the breast. There is no standard treatment protocol and various regimens have been used in different centres without defined conclusions on efficacy^[15]. The prognosis is difficult to make owing to the lack of long term survival data among such patients. The prognosis was poor in primary NEC of the lung and also in metastatic mammary neuroendocrine tumours. The prognosis of the disease in the breast could be better in tumors detected at a smaller size, without lymph node involvement and without hormonal sensitivity^[16]. In our case, the diagnosis of SCNEC of the breast was made by immunohistochemical examination with absence of insitu component and absence of the pathology other than the breast. Neoadjuvant chemotherapy was preferred due to the nature of the locally advanced disease but showed no response to the usual breast cancer chemotherapy regimen. The myocutaneous flap was used to cover the area after extensive removal of the involved breast skin.

CONCLUSION

Small cell neuroendocrine carcinoma of the breast is a rare disease with poor prognosis. There is no standard treatment protocol. More case reports regarding the management are needed.

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Case Report

Transnasal Endoscopic Resection of Humongous Nasal Pleomorphic Adenoma: Case Report and Literature Review

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ABSTRACT

Eleven cases of transnasal endoscopic resection of unilaterally occurring pleomorphic adenomas have thus far been reported. This in part is due to the rarity of the disease, but could also reflect on the technical challenge required for wide en bloc excision of such tumors from a relatively small and narrow nasal cavity. We report the case of a large

pleomorphic adenoma of the nose, occupying both nasal cavities with destruction of the cartilaginous nasal septum, removed completely through an endoscopic transnasal approach. To our knowledge, this is the first reported case of endoscopic resection of a humongous pleomorphic adenoma arising from both sides of the nasal septum.

KEY WORDS: endoscopic approach, nasal cavity, transnasal, tumor

INTRODUCTION

Although it is the most common benign tumor of the major salivary glands, pleomorphic adenoma (PA) accounts for only 8% of all minor salivary gland tumors^[1]. Intranasal PA is extremely rare and usually arises from the nasal septum. Surgical resection is the modality of choice for management^[2]. There have been many approaches described in the literature to achieve complete en bloc resection of this tumor with clear margins^[2-3]. Large tumors occupying both nasal cavities are rare and pose a surgical challenge. To date, there are 11 reported cases of transnasal endoscopic resection of nasal PA. These have all been unilateral lesions^[1-14]. We report a case of a large bilateral nasal PA that was successfully resected via transnasal endoscopic approach. In addition, we reviewed the literature regarding PA origin, aetiology, epidemiology, presentation and management with special attention to advantages of transnasal endoscopic surgical approach, histology, and prognosis.

CASE REPORT

An 83-year-old gentleman presented to the otolaryngology clinic complaining of gradual bilateral nasal obstruction for several years associated with

intermittent mild epistaxis. There was no history of facial pain, rhinorrhoea, anosmia, weight loss, fever or previous nasal surgery. Examination revealed a large pink lobulated mass filling both nasal cavities and adherent to the nasal septum (Fig 1). Nasal endoscopy showed no involvement of the nasopharynx. There was no cervical lymph node enlargement and the rest of ear, nose, and throat examination were normal. Computed tomography (CT) scanning of the nose and sinuses revealed a well defined localized non-enhancing soft tissue mass measuring 3.6 x 4 x 3 cm occupying both nasal cavities with some destruction of the cartilaginous nasal septum, but no bony invasion. No calcification was seen within the soft tissue mass (Fig 2). Punch biopsy under local anaesthesia revealed a benign mixed salivary gland tumor.

Under general anaesthesia, the tumour was removed by wide surgical resection through a transnasal endoscopic approach. After decongestion of the nasal mucosa with oxymetazoline nasal spray, the mucosa of the septum, floor of the nose, and the tumour itself were infiltrated with a mixture of 1% lidocaine and 1:200,000 epinephrine. A subperiosteal and subperichondrial dissection from anterior of the nasal septum to define the margins of the tumour was

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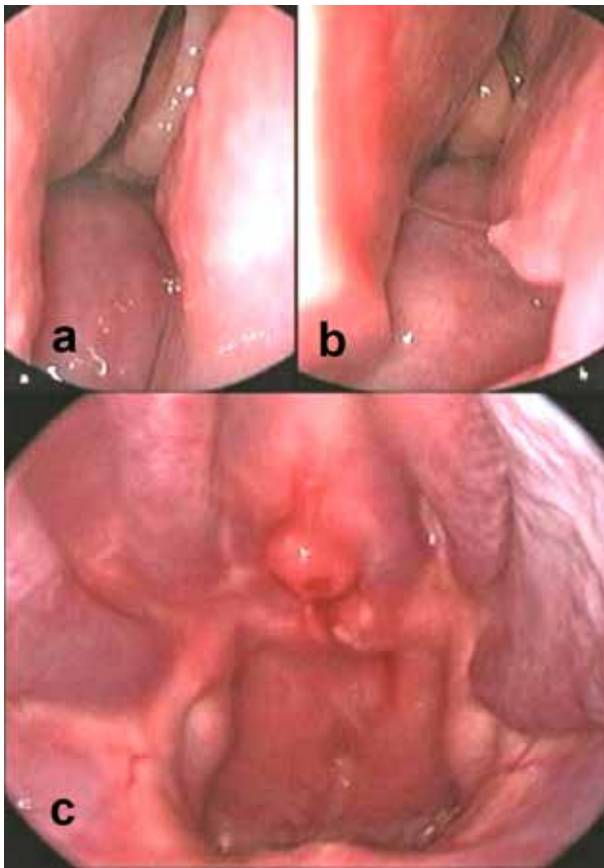


Fig 1: Endoscopic view of the nose showing (a) tumor in right nasal cavity, (b) tumor invading the septum and occupying left nasal cavity, (c) the appearance of the nasal cavity and nasopharynx 6 months after tumor resection

followed by posterior through and through resection of the involved cartilaginous septum. Wide margins were included in dissection. The final area of the septum, which posed technical difficulty in resection, was the mucosa of the nasal floor tethering the nasal septum. This required the insertion of Mayo scissors into one nostril and cutting off this remnant of mucosa with the help of digital palpation from the pharynx. The tumour was dissected en bloc, rotated and delivered anteriorly through a single nostril without need for an ala releasing incision. Haemostasis was secured with bipolar cautery. The nasal cavity was packed with tetracycline impregnated ribbon gauze superiorly and bilateral merocel nasal packs were placed inferiorly along the floor of the nose to prevent the ribbon gauze from falling into the pharynx. The patient was given oral Augmentin. He ran an uneventful post-operative period. Packs were removed at the clinic after 4 days without any complications.

Histopathology report showed a 6 x 5 x 1.5 cm tumour comprising tubular structures lined by epithelial and myoepithelial cells, with the latter entrapped within stromal material of fibromyxoid, collagenous, and intermixed fat. There were some pieces of stromal tissue with lobules of seromucinous glands covered with respiratory epithelium as well as bars of mature native cartilage and focal squamous metaplasia. There was no evidence of malignancy. The final diagnosis was cellular PA.

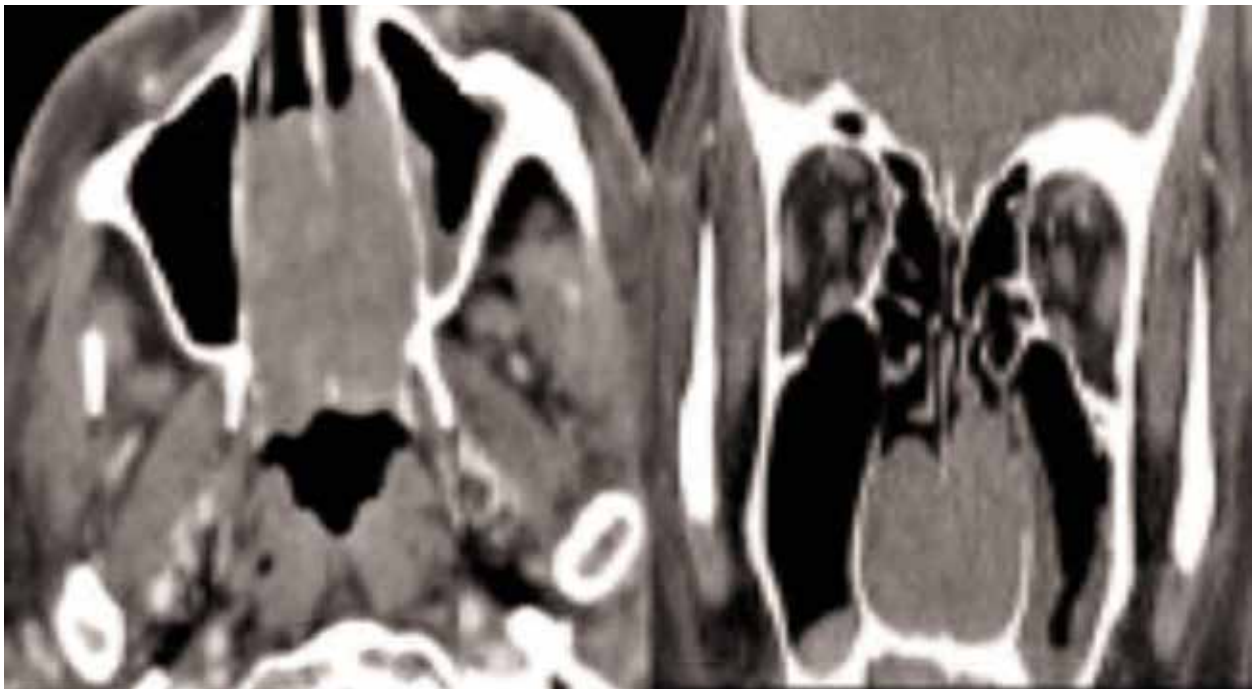


Fig 2: CT scan of the nose (coronal and axial views) showing the tumor involving both nasal cavities and eroding through the nasal septum

At six months follow up, there was no endoscopic evidence of residual or recurrent disease (Fig 1c). The patient was advised to continue a long-term follow-up for the purpose of surveillance for any evidence of recurrence.

DISCUSSION

Pleomorphic adenoma is the most common benign tumor of the major salivary glands^[2-3]. In only 8% of cases, it affects minor salivary glands that are distributed in the various regions of the aerodigestive tract including nose, pharynx, larynx, trachea, and mediastinum^[1,4]. As such, PA of the nasal cavity is extremely rare^[3,5]. Denker and Kahler are accredited for the first reported case of nasal PA in the literature in 1929^[2].

Despite the fact that minor salivary glands are more abundant in the lateral nasal wall, between 80 and 90% of PA of the nose arises from the nasal septum^[6]. In the largest series of 59 cases of nasal PA reported by Wakami *et al*, only 8 adenomas had arisen from the lateral nasal wall^[7]. Various theories were proposed to explain this observation, including the development from un-degenerated remnants of the vomeronasal organ, an epithelium-lined duct in the cartilaginous nasal septum degenerated in the early foetus^[8]. Development from ectopic embryonic epithelialized cells on the nasal septal mucosa impeded during migration of the nasal buds have been suggested by Ersner and Saltzman as the precursor of PA from nasal septum^[8]. The exact reason is yet unknown.

The aetiology of PA nose is a subject of controversy as well. Evans and Cruikshank thought that it originated directly from mature salivary gland tissue at the nose^[8]. Dawe proposed a viral infection with human papilloma virus (HPV) as an aetiology for nasal PA^[9]. Later, in 1998, research investigating the presence of different viruses including HPV and Epstein Barr virus (EBV) in salivary gland tumors was done and out of 19 PAs including one arising from the nose, EBV was detected in PA nose while HPV was not retrieved in any of the other tumors^[10]. Recently, Vageli *et al* further studied the relationship between HPV and different parotid lesions and was able to detect HPV16 DNA in 7 out of 9 cases, 2 of which were PAs^[11].

The majority of nasal PA cases present between the third and sixth decades of life^[2,4,12]. Women are more frequently affected than men^[2]. The most common clinical presentation is progressive nasal obstruction associated with infrequent epistaxis^[1-14]. Other uncommon presenting symptoms include nasal mass, mucopurulent nasal discharge, and epiphora^[6].

Examination usually reveals a smooth, greyish pink, non-tender, broadly based, unilateral or bilateral

soft nasal mass^[3,5,8]. It varies in size from 0.5 cm to over 7cm in its largest diameter^[1-4]. Our reported case measured 6 x 5 cm and was occupying both nasal fossae with an origin from both cartilaginous nasal septum as well as floor of the nose bilaterally.

CT scan is useful in estimating the actual size and extent of the tumour, demonstrating its origin, and excluding any surrounding bony or soft tissue destruction^[4]. A well-defined, heterogeneous, expanding, multilobulated, poorly enhancing, soft tissue mass arising from either the nasal septum or from the lateral wall of the nose is the most common CT scan feature of nasal PA^[1,4,5,12]. Other features that could be seen, although more often associated with malignant tumors, include presence of calcification, surrounding tissue or bony destruction, and cartilaginous nasal septum involvement^[4,12]. In this reported case, an unusual CT scan feature showing destruction of the nasal septum was noted.

According to Ozturk *et al*, MRI is a more reliable diagnostic tool for intranasal PA since it can assess the relationship of the PA with adjacent structures in several anatomic planes^[4]. PAs usually have heterogeneous, low-to-intermediate signal intensity on T1-weighted images with heterogeneous contrast enhancement and intermediate-to-high signal intensity and occasional hypointense capsule on T2-weighted images^[4].

The general consensus for management of benign salivary gland tumors is wide local resection with histologically clear margins^[2]. Various approaches for nasal PA resection have been described in the literature. These include lateral rhinotomy, mid-facial degloving, external rhinoplasty, intranasal, and transnasal endoscopic approach^[2,3,8]. The choice of surgical approach mostly depends on tumor size, location, extent, and the surgeon's skills^[8].

With the advancement of endoscopic sinus surgery, reports of successful removal of different benign sinunasal tumors have been published. Only 14 cases of endoscopic resection of nasal PA has been reported so far, all of which were limited to one side of the nose^[1-14]. To our knowledge, this is the first reported case of bilateral nasal PA eroding through the cartilaginous septum and successfully removed via endoscopic transnasal approach. Similar to other proponents of the endoscopic approach, we found it to be safe, enabling good visualization of the margins, total surgical excision with minimal blood loss, less post-operative pain, shorter hospital stay, and avoidance of unnecessary soft tissue resection^[1,4,8]. In addition, endoscopic resection provides great magnification and thus better control of actual bleeding sites. Furthermore, it spares the patient external wounds, suture removal, and facial scars^[15]. Most importantly,

it is associated with less morbidity and increased patient satisfaction^[1]. Endoscopic debulking of the tumor for relief of symptoms and improvement of patient' quality of life has been described in recurrent aggressive cases with skull base erosion^[15]. Endoscopic approach joined with computer-assisted surgery (CAS) using three dimensional navigation system, although not a substitute for thorough sinonasal anatomic knowledge, can be substantially helpful, especially in difficult cases with high risk for complications, revision cases where normal anatomic landmarks are absent as well as in cases where skull base or orbital erosion is suspected^[13,15]. In this reported case, CAS was not utilized as the tumor was confined to the nasal cavity with no skull base nor orbital erosion.

Although PA of the parotid gland tends to recur in 50% of cases, PA of the nose has a reported local recurrence rate of 2.4% to 10%^[1,4]. This could be due to incomplete tumor margins resection^[1]. Compagno and Wong reported 7.5% recurrence rate in their 40 PA nose patients. They believed that it is due to the high amount of myxoid stroma of the tumor that could have spilled into the surgical field^[6,12]. Wakami *et al* reported a recurrence rate of 5.1% among 59 cases of PA nose. He emphasized the importance of differentiating tumor recurrence from malignant transformation of the tumor which occurred in four patients (6.8%)^[7].

Histologically, intranasal pleomorphic adenoma shows high cellularity as compared with the major salivary gland tumors^[1-12]. They are characterized by epithelial tissue mixed with myxoid, chondroid, or mucoid tissues and few or no stroma^[2].

The epithelial cells are usually small, oval shaped, and often arranged in cords or occasionally in small acinous structures^[9]. The epithelial component has a potential for malignant transformation and metastasis^[3]. Immunohistochemical staining is positive for various cytokeratines, S100 protein, glial fibrillary acid protein (GFAP), Vimentine, and smooth muscle actin (SMA)^[8]. This is, in fact, similar to immunohistochemical findings of PA of major salivary glands^[3].

Although benign, PA may occasionally behave in a malignant fashion leading to regional and distant metastasis in the liver, lung and bone. In the literature, there are ten reported cases of metastasis from parotid PA and 3 other cases of metastasis from minor salivary gland PAs^[14]. In one reported case, metastasis from nasal septal PA to ipsilateral submandibular lymph-node developed 17 years after the first diagnosis. However, microscopic features of both primary and metastatic lesions were histopathologically benign. This was explained theoretically as iatrogenic spread from either incomplete excision or inadvertent

disruption of the tumor with subsequent spread through haematogenous or lymphatic routes. Iatrogenic theory, however, failed to explain the delayed onset of metastasis.

Generally, PA has a 6% potential for malignant transformation^[8]. In the 59 nasal PA cases reported by Wakami *et al*, 6.8% (4 cases) developed malignancy on follow up^[7]. Long-term follow-up is therefore necessary for early detection of tumor recurrence, metastasis, or development of malignancy^[8].

CONCLUSION

Pleomorphic adenoma of the nose is rare but remains a differential diagnosis for benign nasal tumors. The recommended management is wide surgical excision with clear margins. Many surgeons prefer a transnasal endoscopic approach as this allows resection under direct vision with complete control of margins, rapid postoperative recovery, and short hospital stay. A larger series of endoscopically resected tumors with a longer follow-up is required to establish if recurrence rates in these cases match or improve upon that of open approach resections.

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Case Report

Primary Epithelioid Angiosarcoma of the Small Intestine Mimicking Multiple Myeloma: A Rare Diagnostic Entity with a Unique Clinical Presentation

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ABSTRACT

Angiosarcomas are aggressive and highly malignant tumors of endothelial cells, occurring mainly in the skin or superficial soft tissue of the head, neck and the breast. Primary angiosarcoma of the small intestine is extremely rare and very few cases have been reported in literature. We herein describe a case of primary duodenal epithelioid angiosarcoma with metastasis to the abdominal lymph nodes, lumbar vertebra, sacrum and iliac crest, in a 63-year-old gentleman. On initial evaluation, the clinical findings appeared suspicious of

multiple myeloma. The patient was subsequently diagnosed as duodenal angiosarcoma based on radiology, endoscopy, histopathology and immunohistochemistry findings. Awareness of this aggressive and rapidly progressive entity is important. Due to its rarity, its clinical presentation can be misinterpreted at the outset, as it was in our case, leading to delayed diagnosis and management. To the best of our knowledge, this is the first report of primary angiosarcoma of the small intestine from the Middle East.

KEYWORDS: angiosarcoma, epithelioid, hemangiosarcoma, multiple myeloma, small intestine

INTRODUCTION

Angiosarcomas are high grade malignant vascular neoplasms that occur primarily in the skin, soft tissue and breast, occasionally in liver, spleen and heart^[1-3]. They are extremely rare in the intestine. We report a case of a primary duodenal epithelioid angiosarcoma with metastasis, mimicking as multiple myeloma, presenting with back pain, osteolytic bone lesions, anemia, thrombocytopenia and lymphadenopathy.

CASE REPORT

A 63-year-old male came with back pain, occasional epigastric pain, weakness and weight loss since 5 months and melena since 2 weeks. Physical examination was unremarkable and he was hemodynamically stable. There was no organomegaly.

Blood tests revealed severe hypochromic normocytic anemia and thrombocytopenia. Peripheral smear showed rare atypical plasmacytoid-like mononuclear cells. Radiology demonstrated multiple osteolytic lesions in the pelvic bones and lumbar vertebra with a compression fracture and several large metastatic type mesenteric lymph nodes (Fig 1). There was mild bilateral pleural effusion. No ascites, intra-abdominal bleeding/hematoma or soft tissue mass was identified. Serum tumor markers CA-125, AFP, CEA, CA 15-3 and CA19-9 were not significantly elevated. Multiple myeloma was considered as a probable diagnosis, however tests for Bence Jones proteins in urine, serum calcium levels and electrophoresis were normal. A bone marrow aspirate with trephine biopsy was done and showed numerous large pleomorphic mononuclear

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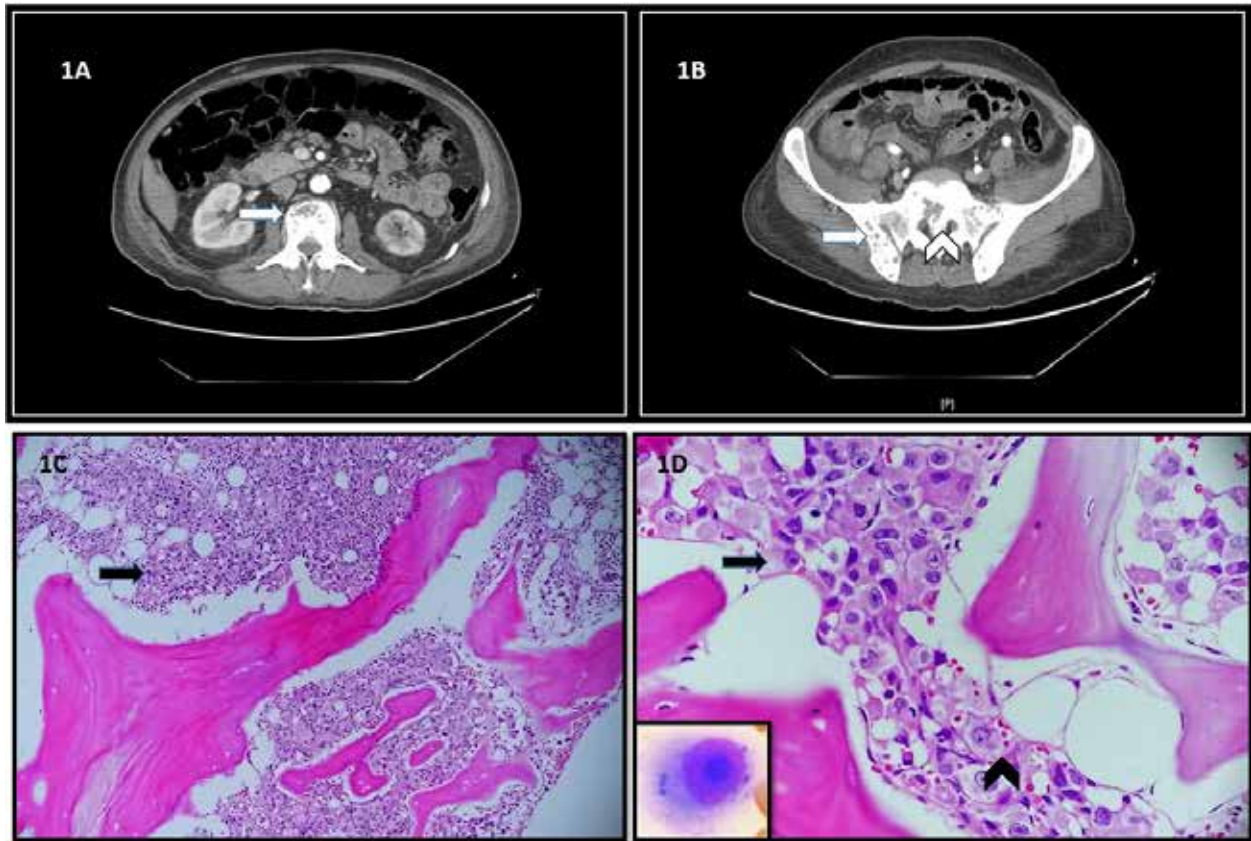


Figure 1 A, B, C & D: Computed tomography scan, axial plane (A and B) of the abdomen showed several enlarged lymph nodes and osteolytic lesions in the lumbar vertebra (arrow in 1A), in the sacrum (arrowhead) and the iliac crest (arrow in 1B). No associated soft tissue mass is seen. The bowel segments show no obvious mass. (C and D) Light microscopy photograph of the bone marrow trephine biopsy shows irregular bony spicules with intervening marrow space. The marrow space is expanded and infiltrated by large poorly differentiated neoplastic cells (arrows), corresponding to the osteolytic lesions. Some cells show intracytoplasmic vacuoles containing red blood cells. (H & E stain; $\times 100$ and $\times 400$ respectively.) Inset: the bone marrow aspirate shows similar cells (Giemsa stain; $\times 400$.)

cells resembling plasmablasts with abundant cytoplasm, large eccentric nuclei and multiple distinct nucleoli (Fig 1). In some cells, the cytoplasm appeared vacuolated. The myeloid, erythroid and megakaryocytes precursors were markedly reduced but appeared normal. On immunohistochemistry, the atypical cells were positive for vimentin and CD31. The CD38, CD138, CD56, CD34 and CD20 were negative. It was reported as infiltration of bone marrow by a non-hematopoietic malignancy.

The patient received multiple red blood cells and platelets transfusion. His melena became worse and the hemoglobin and platelet levels continued to drop. Colonoscopy and endoscopy were performed. The colonoscopy showed no significant abnormality. The endoscopy showed a pin point ulcer in the gastric body and several polypoidal, ulcerated and hemorrhagic nodules in the third part of duodenum (Fig 2). Biopsies were taken from both the gastric and the duodenal

lesions. The gastric biopsy showed mild chronic active inflammation only with no *Helicobacter pylori* or malignancy. The biopsy from the duodenal lesion showed sheets of poorly differentiated malignant cells similar to those in the bone marrow biopsy: large epithelioid cells with eccentric nuclei, prominent nucleoli and abundant cytoplasm (Fig 2). Some cells show intracytoplasmic rudimentary lumen containing occasional red blood cells. On immunohistochemistry, these cells, like those in the bone marrow sample, were diffusely positive with vimentin and CD31 (Fig 3). In addition, they were focally positive with CK cocktail, CK 8/18, CD68 and CD138. There was no loss of INI-1 expression. Kappa, Lambda, CD34, CD38, D2-40, EMA, CEA, HMWCK, S100, HMB45, CD45, CD30, ALK1, MPO, Desmin, SMA, TTF1, Synaptophysin, NSE, CD117, DOG1, EBV AND HHV-8 were negative. A diagnosis of primary duodenal epithelioid angiosarcoma with metastases to bone and abdominal

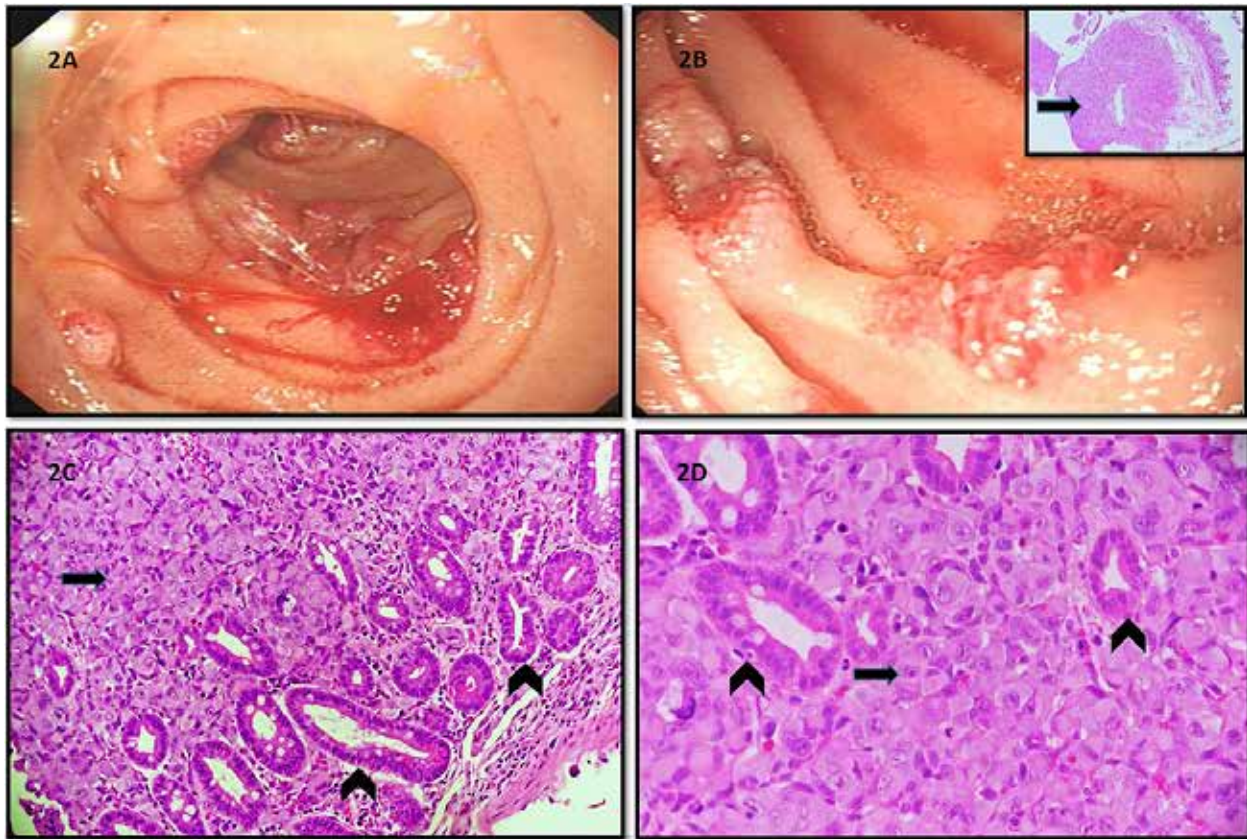


Figure 2 A, B, C & D: Endoscopic images (A & B) show multiple raised lesion in the third part of duodenum with active bleeding. Inset: light microscopy photomicrograph of the lesion shows a tumor nodule (arrow) with overlying duodenal mucosa with villi. (H & E stain; x40.) (C and D) Light microscopy photograph of the duodenal tumor shows sheets of large poorly differentiated tumor cells (arrows) displacing and replacing the duodenal glands (arrowheads). The tumor cells have abundant eosinophilic cytoplasm, eccentric nuclei and prominent nucleoli. Some red blood cells are noted in between the tumor cells. (H & E stain; x200 and x400 respectively.)

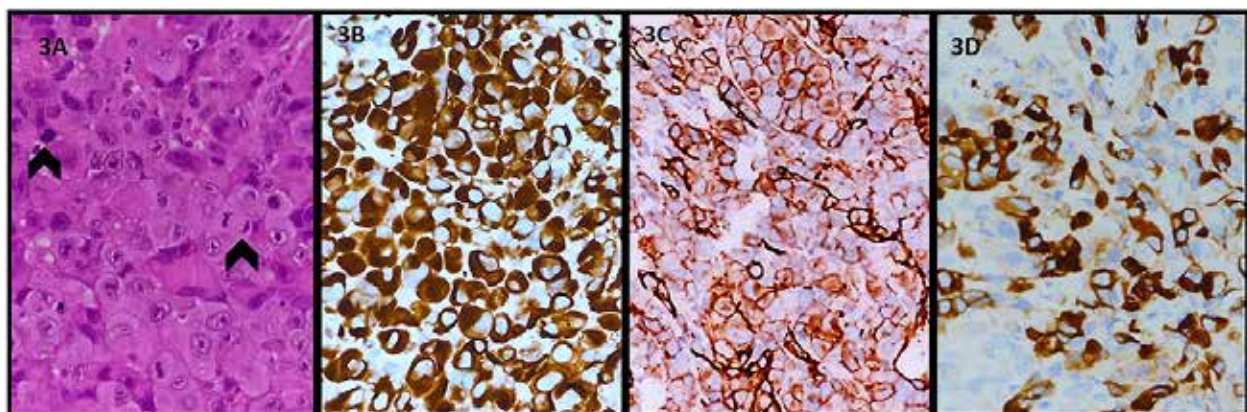


Figure 3 A, B, C & D: (A) Light microscopy photograph of sheets of pleomorphic tumor cells with abundant eosinophilic cytoplasm, large nuclei and prominent nucleoli. Few mitotic figures are also seen (arrowheads). (H & E stain; x400.) Immunohistochemistry staining study of the tumor cells show (B) diffuse cytoplasmic positivity with Vimentin (x400), (C) diffuse cell membrane positivity with CD31, confirming the endothelial nature of the tumor cells (x400) and (D) focal cytoplasmic positivity with Cytokeratin 8/18, indicating the epithelioid differentiation of the tumors cells. (x400.)

lymph nodes was made. The patient was unfit for surgery. He was provided supportive care and died within 10 days of diagnosis, before any adjuvant therapy could be planned.

DISCUSSION

Angiosarcomas account for less than 1% of all soft tissue sarcomas^[1-3]. The most common sites include skin and soft tissue^[1]. The gastrointestinal tract (GIT) is an extremely rare site for primary angiosarcoma. Risk factors for angiosarcomas include radiation, toxins (e.g. vinyl chloride, Thorotrast contrast media, arsenic, anabolic steroids and foreign bodies), chronic lymphedema and some familial syndromes (e.g. neurofibromatosis NF1, mutated BRCA1-2, Mafucci and Klippel-Trenaunay syndromes)^[2]. Our patient had no such history. Diagnosis of angiosarcoma is made on histopathology. The microscopic features of angiosarcoma vary between cases, ranging from subtle to frank features of malignancy and of vascular differentiation. In our case, the cells were frankly malignant but the features of vascular differentiation were very subtle. Typically, the malignant endothelial cells are fusiform, lining vascular channels that dissect and infiltrate the tissue. As the cells become less differentiated, the vascular spaces become less obvious and the malignant cells more pleomorphic with brisk mitosis, hemorrhage and necrosis. In the epithelioid variant, the cells are plump and rounded, making differentiation from anaplastic carcinoma, non-Hodgkin lymphoma, other sarcomas and melanoma difficult. In such cases, immunohistochemistry study is essential for diagnosis. Angiosarcomas are typically positive for endothelial markers CD34, CD31, and FLI-1 and occasionally for D2-40 and vWF. The epithelioid variant is also positive for cytokeratins, adding to diagnostic confusion with poorly differentiated carcinomas^[2].

There are very few cases of small intestinal angiosarcoma reported in literature^[1,4,5]. Ni *et al* in their case report, identified and detailed 27 articles that reported small intestinal angiosarcomas^[5]. In it, patients' age ranged from 25 - 87 years, majority being over 60 years with slight male preponderance (64.3%), 9 patients had history of radiation exposure and 1 had history of exposure to polyvinyl chloride. The common symptoms were melena, abdominal pain, intestinal obstruction, anemia, weight loss and fatigue. Surgical resection was performed in almost all patients. Patient survival ranged from 6 weeks to 2 years from diagnosis.

Management for angiosarcomas include surgical excision with adjuvant radiotherapy and/or chemotherapy. The efficacy of chemotherapy for angiosarcoma is still uncertain^[2].

Angiosarcomas have poor prognosis, especially in case of epithelioid variant or primary small intestinal tumors, as most patients expire within months of diagnosis^[2,6,7]. Older age, higher tumor grade, necrosis and metastases are poor prognostic indicators^[4,7]. Metastasis can be to lungs, liver, bone, soft tissue and lymph nodes^[2]. Imaging is essential to detect tumor extent/metastases and to define the overall prognosis^[2]. The general 5-year survival for angiosarcomas ranges from 30 - 40%^[6,8].

CONCLUSION

Primary duodenal angiosarcoma is an extremely rare and highly aggressive tumor with very poor prognosis. In spite of its rarity, this entity should be a diagnostic consideration in elderly patients with recurrent GI bleeding, not responding to routine management. An index of suspicion may ensure an early diagnosis and timely surgery, thereby improving the survival rate.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Gallbladder Mucus Plug Mimicking Ascaris Worm: An Ambiguous Cause of Biliary Colic

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Biliary colic is a visceral pain caused by attempts of the gallbladder or bile duct to overcome the obstruction in the cystic duct or ampulla of Vater. Obstruction can be due to different etiologies such as stone, mass, worm, and rarely by mucus plug. We report the case of a 31-year-old gentleman who presented with recurrent biliary colic and weight loss. Work-up showed linear calcifications in the gallbladder extending to the common bile duct suggesting hepatobiliary ascariasis. Further investigations including stool analysis, upper endoscopy, endoscopic ultrasonography (EUS), and endoscopic retrograde cholangiopancreatography (ERCP) did not support our provisional diagnosis. Laparoscopic cholecystectomy was performed. Histopathological finding was grossly ambiguous; a rope-like mucus plug resembling ascaris worm was noted. The patient's condition improved instantly after the procedure. To our knowledge, we are reporting the first case in the English literature describing this unique entity of symptomatic gallbladder disease to increase awareness and improve its management.

Torsion of huge wandering accessory spleen. Case report and review of literature

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INTRODUCTION: Accessory spleens are found in 10-15% of the population, and are even more prevalent in patients with hematological disorders (Rudowski, 1985). It infrequently may become symptomatic due to torsion, spontaneous rupture or hemorrhage which may lead to death. Torsion of an accessory spleen is extremely rare, and requires prompt medical attention^[2] (Coote *et al.*, 1999).

PRESENTATION OF CASE: We report the case of a 27-year-old Mediterranean lady with thalassemia trait, who presented to the emergency department with an acute surgical abdomen due to torsion of a giant accessory spleen, measuring 13 cm. She was diagnosed with the aid of ultrasound and computed tomography (CT) scan and was treated surgically through resection of the spleen.

DISCUSSION AND CONCLUSION: Torsion of an accessory spleen is not common, and is the surgical indication in about 0.2-0.3% of splenectomies (Mortele *et al.*, 2004). It has variable clinical presentations, and is a difficult preoperative diagnosis due to lack of specificity of symptoms. Accessory spleens are usually smaller than 3 cm, with few cases being reported as larger than 10cm larger accessory spleens have a higher rate of torsion. Knowledge of this pathology, and familiarity with its radiological findings are fundamental to accurately diagnosing and managing this challenging condition.

Molecular Screening Versus Phenotypic Susceptibility Testing of Multidrug-Resistant *Mycobacterium tuberculosis* Isolates for Streptomycin and Ethambutol

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Proper management of multidrug-resistant tuberculosis (MDR-TB) requires accurate drug susceptibility testing (DST) of *Mycobacterium tuberculosis* isolates to other (ethambutol [EMB], pyrazinamide, and streptomycin [SM]) first-line drugs. This study compared the performance of *Mycobacterium* Growth Indicator Tube (MGIT) 960 system for DST of MDR-TB isolates with polymerase chain reaction (PCR) sequencing of *embB*, *rpsL*, and *rrs* genes for detecting resistance to EMB and SM. MDR-TB strains ($n = 60$) and 25 pansusceptible *M. tuberculosis* isolates collected during 2011-2016 were tested. Phenotypic DST was performed by MGIT 960 system by using SIRE drug kit. EMB and SM resistance-conferring mutations in *embB* and *rpsL+rrs* genes, respectively, were detected by PCR sequencing. No mutations were detected in pansusceptible isolates. Among 60 MDR-TB strains, 35 of 40 SM-resistant and none of 20 SM-susceptible isolates contained *rpsL* and/or *rrs* mutations ($\kappa = 0.82$, very good agreement). However, all 18 EMB-resistant MDR-TB strains and 33 of 42 EMB-susceptible MDR-TB strains contained an *embB* mutation ($\kappa = 0.14$, poor agreement). Thus, 40 of 60 (67%) and 35 of 60 (58%) isolates were resistant to SM ($p = 0.451$), while 18 of 60 (30%) and 51 of 60 (85%) isolates were resistant to EMB ($p = 0.000$) by MGIT 960 system and PCR sequencing, respectively. MGIT 960 system showed acceptable performance for DST for SM; however, it performed poorly for EMB as many MDR-TB strains with *embB* mutations, which confer low-level resistance to EMB, were detected as EMB susceptible. Molecular screening for resistance-conferring mutations in *embB* gene is thus superior to MGIT 960 system when accurate EMB susceptibility results are needed for proper management of MDR-TB patients.

Resistance-Associated Mutations and Polymorphisms among Integrase Inhibitor-Naïve HIV-1 Patients in Kuwait

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OBJECTIVES: Resistance-associated mutations (RAMs) in the integrase of different HIV-1 subtypes were investigated in a cohort of patients never exposed to integrase strand transfer inhibitors (INSTIs).

METHODS: The viral RNA was extracted from plasma samples of 53 INSTI-naïve patients, and the integrase genetic region was sequenced and analyzed for subtype assignment and drug resistance.

RESULTS: The median viral load at sampling was 5.28×10^4 RNA copies/mL. Bayesian phylogenetic analysis showed 85% of the HIV-1 isolates were non-B subtypes, with a predominance of subtypes C (22.6%) and CRF01_AE (26.4%). A total of 52 and 110 mutations were found in the integrase region of HIV-1 B and non-B subtypes, respectively. Nonpolymorphic INSTI-RAMs were not detected in this study. However, the accessory mutation E157Q was found in 1 patient with CRF02_AG, and the polymorphic mutations L74M/I that may contribute to a reduced susceptibility to INSTIs in the presence of major mutations were observed in 6 (13.3%) patients with non-B subtypes and 1 (12.5%) patient with the B subtype. Polymorphic mutations at positions known to harbor primary and accessory RAMs were also detected in this study.

CONCLUSION: Our results highlight the importance of monitoring the emergence of INSTI-RAMS before and after the initiation of INSTI-based therapy.

Burden of migraine in a Kuwaiti population: a door-to-door survey

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BACKGROUND: Migraine prevalence and disability imprints on Kuwaiti population are underreported. We aimed to measure the prevalence of migraine and to assess its burden in Kuwait.

METHODS: A cross-sectional community-based study was conducted which included biologically unrelated Kuwaiti adult population aged 18-65 years. They were randomly recruited from all six governments of Kuwait using stratified multistage cluster sampling. Trained interviewers visited the samples in door-to-door approach. The Headache-Attributed Restriction, Disability, and Social Handicap and Impaired Participation (HARDSHIP) questionnaire was used to collect the data. Demographic enquires were followed by diagnostic and disability questions.

RESULTS: A total of 15,523 subjects were identified; of whom 3588 (23%) were diagnosed as episodic migraine and 845 (5.4%) as chronic headache. Prevalence of episodic migraine was 31.71% in female versus 14.88% in males ($P < 0.01$) with a mean age of 34.56 ± 10.17 years. Most of migraine cohort (64.4%) sought medical advice with respect to their migraine headaches and the majority (62.4%) were seen by general practitioners (GPs) while 17.2% were assessed by neurologists and 3.7% was seen by other specialties. Tension type headache and sinus-related headaches were diagnosed in 8.9% and 2.1% of migraine subjects respectively. The majority (94.6%) of migraine subjects used symptomatic drugs for headache attacks, whereas 39.9% were taking preventive medication. In the preceding 3 months to the survey, subjects with episodic migraine had lost a mean of 1.97 days from their paid work or school attendance compared to 6.62 days in chronic headache sufferers ($P < 0.001$). Additionally, subjects with episodic migraine lost a mean of 1.40 days from household work compared to 5.35 days in subjects with chronic headache ($P < 0.001$). Participants with episodic migraine and chronic headache missed a mean of 2.81 and 3.85 days on social occasions, in the preceding 3 months ($P < 0.001$).

CONCLUSIONS: Migraine in Kuwait is highly prevalent and it has a significant impact on activity of daily living, schooling/ employment and social occasions of patients. Accurate diagnosis, effective abortive and preventive treatments of migraine are paramount to improve quality of life and as well as cost saving.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2018; 50 (1): 121 - 132

18th International Congress on **Infectious Diseases**

Mar 1 - 4, 2018

Argentina / Buenos Aires

Contact: International Society for Infectious Diseases

Phone: 617-277-0551

Fax: 617-278-9113

Email: info@isid.org

Laboratory Aspects of **Haemoglobinopathy**

Diagnosis

Mar 1, 2018

United Kingdom / London

Contact: Mandy Sale, Continuing Professional Development, Imperial College London

Phone: +44-20-3313-4017

Email: a.sale@imperial.ac.uk

24th Butters-Kaplan West Coast **Neuropsychology** Conference

Mar 1 - 4, 2018

United States / California / San Diego

Contact: Maureen Helinski Clarke, Continuing Medical Education, UC San Diego

Phone: 858-534-3940

Email: ocme@ucsd.edu

13th Annual **Brain Injury Rehabilitation** Conference

Mar 2 - 3, 2018

United States / California / San Diego

Contact: Scripps Conference Services & CME

Phone: 858-678-6400

Email: med.edu@scrippshealth.org

5th International Conference on **Nutrition and Growth**

Mar 1 - 3, 2018

France / Paris

Contact: Josh Margo, Kenes Group

Phone: +972 3-972-7450

Email: jmargo@kenes.com

22nd Annual International Congress on **Hematologic Malignancies**[®]: Focus on Leukemias, Lymphomas & Myeloma

Mar 2 - 4, 2018

United States / Florida / Hollywood

Contact: Physicians' Education Resource, LLC

Phone: 609-378-3701

Fax: 609-257-0705

Email: info@gotoper.com

6th International **Child and Adult Behavioral Health** Conference

Mar 1 - 3, 2018

United Arab Emirates / Abu Dhabi

Contact: Saranya Jinu, Diaedu Management Consultancy

Phone: +971-4-453-2975

Email: sara@diaedu.com

Genomic Instability and Gene Therapeutics in Neurological Diseases 2018

Mar 5 - 8, 2018

Mexico / Cancun

Contact: Conference Manager, Fusion Conferences

Phone: +44-16-3872-4137

Email: admin@fusion-conferences.com

8th Emirates **Diabetes & Endocrine** Congress (EDEC)

Mar 1 - 3, 2018

United Arab Emirates / Dubai

Contact: Kris Olarte, Senior Marketing Executive, MCI Middle East

Phone: +971-4-311-6300

Fax: +971-4-311-6301

Email: kris.olarte@mci-group.com

What Babies Need: A Research Update on **Infant Feeding** & Introduction of Solids

Mar 5, 2018

United Kingdom / London

Contact: Verity Cotton, Organizer, Royal Society of Medicine

Phone: +44-20-7290-3947

Email: maternity@rsm.ac.uk

Intermediate Skills in Laparoscopic Surgery

Mar 6 - 7, 2018

United Kingdom / London

Contact: Education Team, Royal College of Surgeons of England

Email: education@rcseng.ac.uk

18th World Congress of the International Society of Gynecological Endocrinology

Mar 7 - 10, 2018

Italy / Florence

Contact: Congress Secretariat, Biomedical Technologies

Phone: +39-70-340-293; Fax: +39-70-307-727

Email: info@btcongress.com

20th Annual Conference of the International Society for Bipolar Disorders

Mar 7 - 10, 2018

Mexico / Mexico City

Contact: Ron Marcovici, Mr., Kenes Group

Phone: 011-41-2-2908-0488

Email: rmarcovici@kenes.com

8th SEHA International Neonatology Conference

Mar 8 - 10, 2018

United Arab Emirates / Abu Dhabi

Contact: Afsal Ahmad, MENA Conference

Phone: +971-2-491-9888

Email: afsal@menaconference.com

Medicine - Transformation through the 100,000 Genomes Project

Mar 8, 2018

United Kingdom / London

Contact: Royal College of Physicians

Phone: +44-20-3075-2389

Email: conferences@rcplondon.ac.uk

2nd International Diabetes Summit

Mar 9 - 11, 2018

India / Pune

Contact: Ms Nandini Ganatra, Chellaram Diabetes Institute

Phone: +91-20-6683-9767; Fax: +91-20-6683-9701

Email: ids@cdi.org.in

4th International Conference on Hematologic Malignancies at Older Age: Biology & Therapy

Mar 9 - 11, 2018

France / Mandelieu

Contact: Camille Frank, Meeting Coordinator, European School of Haematology

Phone: +33-1-5727-6843; Fax: +33-1-5727-6838

Email: camille.frank@univ-paris-diderot.fr

2018 Ottawa International Conference on Medical Education

Mar 10 - 14, 2018

United Arab Emirates / Abu Dhabi

Contact: Conference Secretariat, Meeting Minds Experts

Phone: +971-4-427-0492

Email: pco@ottawa-icme2018.com

2018 Tropical Medicine Excursion to Uganda

Mar 11 - 23, 2018

Uganda / Entebbe

Contact: Kay Schaefer, MD, Tropical Medicine Excursions

Phone: +49-152-5569-8101

Advances in Alzheimer's & Parkinson's Therapies

AAT-AD/PD Focus Meeting

Mar 15 - 18, 2018

Italy / Turin

Contact: AAT-AD/PD Secretariat, Kenes Group on Behalf of the AAT-AD/PD Focus Meeting

Phone: +972-3-972-7500

Email: aatadpd@kenes.com

International Conference on Large Vessel Vasculitis and Related Disorders

Mar 15 - 17, 2018

United States / Minnesota / Rochester (Mn)

Contact: Kari Koenigs, Mayo Clinic

Phone: 507-293-1876

Email: Koenigs.Kari@Mayo.Edu

Email: info@mer.org

Pediatric Imaging: A Comprehensive Review and Innovations

Mar 15 - 17, 2018

United States / Arizona / Scottsdale

Contact: Administrator, Administrator, CME Science

Phone: 650-440-4424

Email: info@cmescience.com

St. Gallen International Gastrointestinal Cancer Conference: Primary Therapy of Early GI Cancers

Mar 15 - 17, 2018

Switzerland / St. Gallen

Contact: St.Gallen Oncology Conferences

Phone: +41-71-243-0032

Email: info@oncoconferences.ch

Society of Interventional Radiology 2018 Meeting

Mar 17 - 22, 2018

United States / California / Los Angeles

Contact: Society of Interventional Radiology

Phone: 703-691-1805; Fax: 703-691-1855

Email: annualmeeting@sirweb.org

Nephrology 2018

Mar 18 - 23, 2018

*United States / Massachusetts / Boston*Contact: Global and Continuing Education,
Harvard Institute of Medicine

Phone: 617-384-8600; Fax: 617-384-8600

Email: ceprograms@hms.harvard.edu

12th Annual Paediatric Clinical Trials

Mar 19 - 20, 2018

United Kingdom / London

Contact: Kyra Williams, SMI Group

Phone: +44-20-7827-6012

Email: kwilliams@smi-online.co.uk

20th Annual Superbugs & Superdrugs

Mar 19 - 20, 2018

United Kingdom / London

Contact: Teri Arri, SMI Group

Phone: +44-20-7827-6000

Email: tarri@smi-online.co.uk

Neonatal Cranial Ultrasound: The Basics and Advanced

Mar 21 - 23, 2018

*United Kingdom / London*Contact: The Symposium Office, Imperial College
London

Phone: +44-20-7594-2150; Fax: +44-20-7594-2155

Email: sympreg@imperial.ac.uk

Royal College of Obstetricians & Gynaecologists

(RCOG) World Congress 2018

Mar 21 - 24, 2018

Singapore / Singapore

Contact: Stella, Mrs, RCOG

Phone: +65-6379-5260 / 5267; Fax: +65-6475-2077

Email: info@rcog2018.com

12th World Congress on Controversies in**Neurology**

Mar 22 - 25, 2018

Poland / Warsaw

Contact: Registration Team, ComtecMed

Phone: 011-972-3-566-6166

Email: cony@comtecmed.com

9th World Congress on Controversies in**Ophthalmology**

Mar 22 - 24, 2018

Greece / Athens

Contact: Natalie, ComtecMed

Phone: +972-3-566-6166

Email: cophy@comtecmed.com

Clinical Endocrinology 2018

Mar 24 - 28, 2018

*United States / Massachusetts / Boston*Contact: Global and Continuing Education,
Harvard Medical School

Phone: 617-384-8600

Email: ceprograms@hms.harvard.edu

Cardiology in Palliative Care

Mar 29, 2018

*United Kingdom / London*Contact: Hatty Grant, Organizer, Royal Society Of
Medicine

Phone: +44-20-7290-2984

Email: palliative@rsm.ac.uk

6th Biennial Schizophrenia International Research

Society Conference: Integrated Prevention &

Treatment - Shifting the Way We Think

Apr 4 - 8, 2018

*Italy / Florence*Contact: Kelly Phy, CMP, Meetings Manager,
Parthenon Management Group

Phone: 615-324-2378; Fax: 615-523-1715

Email: kphy@parthenonmgmt.com

Current Concepts in Limb Loss Management

Apr 5 - 6, 2018

*United States / Pennsylvania / Hershey*Contact: Continuing Education, Penn State College
of Medicine

Phone: 717-531-6483; Fax: 717-531-5604

14th International Cartilage Repair Society World

Congress

Apr 9 - 12, 2018

*China / Macau*Contact: Melanie Twerenbold, Organizer, Cartilage
Executive Office GmbH

Phone: 011-41-44-503-7371; Fax: 011-41-44-503-7372

Email: office@cartilage.org

Strategies in Emergency General Surgery

Apr 10 - 11, 2018

*United Kingdom / Manchester*Contact: Education Team, Royal College of
Surgeons of England

Email: education@rcseng.ac.uk

16th World Congress of Endoscopic Surgery

Apr 11 - 14, 2018

*United States / Washington / Seattle*Contact: Society of American Gastrointestinal and
Endoscopic Surgeons

Phone: 310-437-0544

Email: webmaster@sages.org

2018 Annual Middle East **Otolaryngology**
Conference and Exhibition
Apr 11 - 13, 2018
United Arab Emirates / Dubai
Contact: Informa Life Sciences Exhibitions
Phone: 011-971-4-336-7334
Email: me-oto@informa.com

2018 International **Liver** Congress™
Apr 11 - 15, 2018
France / Paris
Contact: Office, Congress Organisers, European
Association for the Study of the Liver
Phone: 011-41-22-807-0360
Email: ilc.information@easloffice.eu

38th Annual International Society for **Heart & Lung
Transplantation** (ISHLT) Meeting & Scientific
Sessions
Apr 11 - 14, 2018
France / Nice
Contact: ISHLT
Phone: 972-490-9495; Fax: 972-490-9499
Email: meetings@ishlt.org

9th International Conference on **Thrombosis &
Hemostasis Issues in Cancer**
Apr 13 - 15, 2018
Italy / Bergamo
Contact: Organizing Secretariat, Servizi
Congressuali Ed Eventi Culturali
Phone: 011-39-3-524-9899; Fax: 011-39-3-523-7852
Email: info@icthc.com

Plastering Techniques for **Fracture Treatment**
Apr 13, 2018
United Kingdom / Edinburgh
Contact: Education Section, Royal College of
Surgeons of Edinburgh
Phone: +44-13-1527-1600
Email: education@rcsed.ac.uk

11th International Symposium on **Pneumococci and
Pneumococcal Diseases**
Apr 15 - 19, 2018
Australia / Melbourne
Contact: Josh Margo, Kenes Group
Phone: +972-3-972-7450
Email: jmargo@kenes.com

ADIT 2018 | 10th International Conference on
Advances in **Diabetes & Insulin Therapy**
Apr 15 - 17, 2018
Croatia / Dubrovnik
Contact: Maja Svirgelj, ADIT Secretariat, C/O
Amatis Consulting | Meeting | Design - CME
Email: info@adit-conf.org

Surviving and Thriving: A Tool Kit for the **Modern
Primary Care Practice**
Apr 16, 2018
United Kingdom / London
Contact: Lucy Courtney-Bennett, Organizer, Royal
Society of Medicine
Phone: +44-20-7290-3945
Email: gp@rsm.ac.uk

Acute Medicine - London
Apr 18, 2018
United Kingdom / London
Contact: Royal College of Physicians
Email: conferences@rcplondon.ac.uk

Musculoskeletal Ultrasound in **Hemophilia**
Apr 18 - 20, 2018
United States / California / San Diego
Contact: Marlene Zepeda, Continuing Medical
Education, UC San Diego
Phone: 858-534-3940
Email: ocme@ucsd.edu

2018 World Congress on **Osteoporosis,
Osteoarthritis & Musculoskeletal Diseases**
Apr 19 - 22, 2018
Poland / Krakow
Contact: Sophie Leisten
Phone: 011-32-87-852-652
Email: info@humacom.com

14th International Society of **Ultrasound in
Obstetrics & Gynecology** (ISUOG) International
Symposium
Apr 20 - 22, 2018
Greece / Athens
Contact: ISUOG
Phone: 011-44-20-7471-9955; Fax: 011-44-20-7471-9959
Email: info@isuog.org

European **Clinical Case Reports** Congress:
Bridging the Knowledge Gap among Clinical
Disciplines (EUCCR-2018)
Apr 21 - 22, 2018
Austria / Vienna
Contact: Sandra Oberhuber, Mag., European
Society For Translational Medicine (EUSTM)
Phone: +43-1-892-3562
Email: euccr-2018@eutranslationalmedicine.org

25th International **HIV Dynamics & Evolution**
Apr 22 - 23, 2018
United States / Washington / Leavenworth
Contact: Maureen Helinski Clarke, Continuing
Medical Education, UC San Diego
Phone: 858-534-3940
Email: ocme@ucsd.edu

2018 **Osteoarthritis** Research Society International (OARSI) World Congress
Apr 26 - 29, 2018
United Kingdom / Liverpool
Contact: OARSI
Phone: 856-642-4215
Email: info@oarsi.org

Child Abuse Summit: Tips from the Team
Apr 26 - 27, 2018
United States / Minnesota / Minneapolis
Contact: Priyanka Chaduvula, Office of Continuing Professional Development, University of Minnesota Medical School
Phone: 800-776-8636 or 612-626-7600
Fax: 612-626-7766
Email: cme@umn.edu

Educating Family Physicians in **Palliative Care**
Apr 26 - 29, 2018
Canada / Ontario / Kingston
Contact: Continuing Professional Development, Queen's University Faculty Of Health Sciences
Phone: 613-533-2540; Fax: 613-533-6642
Email: cpd.che@queensu.ca

Newborn Behavioural Observations Training 2018
Apr 26 - 27, 2018
United Kingdom / London
Contact: Verity Cotton, Organizer, Royal Society of Medicine
Phone: +44-20-7290-3947
Email: maternity@rsm.ac.uk

Serious Infection and Critical Care in Children
Apr 26 - 27, 2018
United Kingdom / London
Contact: Continuing Professional Development, Imperial College London
Phone: +44-20-7589-5111

Teach the Teacher
Apr 26 - 27, 2018
United Kingdom / London
Contact: Tasha Shaw, Organizer, Royal Society of Medicine
Phone: +44-20-7290-3867; Fax: +44-20-7290-2992
Email: rsmprofessionals@rsm.ac.uk

Writing, Publishing, and Social Media for Healthcare Professionals
Apr 26 - 28, 2018
United States / Massachusetts / Boston
Contact: Global and Continuing Education, Harvard Medical School
Phone: 617-384-8600
Email: ceprograms@hms.harvard.edu

2018 International **Anesthesia** Research Society (IARS) Annual Meeting & International Science Symposium
Apr 28 - May 1, 2018
United States / Illinois / Chicago
Contact: Annual Meeting Education and General Meeting Inquiries, IARS
Email: meetings@iars.org

2018 Summit on National and Global **Cancer** Health Disparities
Apr 28 - 29, 2018
United States / Washington / Seattle
Contact: Tara Shah, Executive Director, Binaytara Foundation
Phone: 360-707-7593; Fax: 360-4499-6271
Email: support@binayfoundation.org

Pulmonary and Critical Care Medicine 2018
Apr 29 - May 2, 2018
United States / Massachusetts / Boston
Contact: Harvard Medical School Global and Continuing Education
Phone: 617-384-8600
Email: ceprograms@hms.harvard.edu

Developing World **Anaesthesia**
Apr 30, 2018
United Kingdom / London
Contact: Royal College of Anaesthetists
Phone: +44-20-7092-1500; Fax: +44-20-7092-1730
Email: info@rcoa.ac.uk

21st European Congress of **Physical & Rehabilitation Medicine**
May 1 - 6, 2018
Lithuania / Vilnius
Contact: Papamichali Dimitra, Registration Department, Goldair Congress
Phone: 011-30-210-327-4570; Fax: 011-30-210-331-1021
Email: info@esprm2018.com

14th International **Mesothelioma** Interest Group (IMIG) International Conference
May 2 - 5, 2018
Canada / Ontario / Ottawa
Contact: IMIG
Email: info@imig.org

Dermatology for GPs
May 2, 2018
United Kingdom / London
Contact: The Symposium Office, Imperial College London
Phone: +44-20-7594-2150; Fax: +44-20-7594-2155
Email: sympreg@imperial.ac.uk

Beyond Surgery: **Otology**, Quizzing the Experts and Medical Jurisprudence
 May 4, 2018
United Kingdom / London
 Contact: Hatty Grant, Organizer, Royal Society of Medicine
 Phone: +44-20-7290-2984
 Email: otology@rsm.ac.uk

Laryngology – Office Based and Complex Diagnoses
 May 4, 2018
United Kingdom / London
 Contact: Hatty Grant, Organizer, Royal Society of Medicine
 Phone: +44-20-7290-2984
 Email: laryngology@rsm.ac.uk

Neurology for the Non-Neurologist
 May 4, 2018
United States / Pennsylvania / Hershey
 Contact: Continuing Education, Penn State College of Medicine
 Phone: 717-531-6483; Fax: 717-531-5604

Ultrasound-Guided Nerve Blocks in **Emergency Medicine**
 May 4, 2018
United States / Florida / St. Petersburg
 Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc
 Phone: 727-363-4500; Fax: 727-363-0811
 Email: learn@gcus.com

Endoscopic Surgery of the Sinuses, Eustachian Tube and Ear
 May 7 - 9, 2018
United States / Massachusetts / Boston
 Contact: Global and Continuing Education, Harvard Medical School
 Phone: 617-384-8600; Fax: 617-384-8600
 Email: ceprograms@hms.harvard.edu

Controversies and Complications in the **Musculoskeletal System**
 May 8 - 11, 2018
Israel / Tel Aviv
 Contact: Department of Radiology, Penn Medicine
 Phone: 800-789-7366

In Kraepelin's Shadow: Historical & Philosophical Foundations of Contemporary Biological **Psychiatry**
 May 8, 2018
United Kingdom / London
 Contact: Ruth Cloves, Organizer, Royal Society of Medicine
 Phone: +44-20-7290-2985
 Email: psychiatry@rsm.ac.uk

9th World Congress of the World Institute of **Pain**
 May 9 - 12, 2018
Ireland / Dublin
 Contact: Ron Marcovici, Kenes Group
 Phone: 011-41-22-908-0488
 Email: rmarcovici@kenes.com

Ethics and Law for **Anaesthetists**
 May 9, 2018
United Kingdom / London
 Contact: Royal College of Anaesthetists
 Phone: +44-20-7092-1500; Fax: +44-20-7092-1730
 Email: info@rcoa.ac.uk

HAVS and other Work Related **Neurovascular Conditions**
 May 9, 2018
United Kingdom / London
 Contact: Occupational Medicine Section, Royal Society of Medicine
 Phone: +44-20-7290-2987
 Email: occupational@rsm.ac.uk

Roadblocks to Effective Treatment of Early Inflammatory **Arthritis**
 May 9, 2018
United Kingdom / London
 Contact: Ruth Cloves, Organizer, Royal Society of Medicine
 Phone: +44-20-7290-2985
 Email: rheumatology@rsm.ac.uk

Pre-Hospital and Emergency Department **Resuscitative Thoracotomy**
 May 10, 2018
United Kingdom / London
 Contact: Education Team, Royal College of Surgeons of England
 Email: education@rcseng.ac.uk

Systematic Training in **Acute Illness Recognition** and Treatment for Surgery
 May 12, 2018
United Kingdom / London
 Contact: Education Team, Royal College of Surgeons of England
 Email: education@rcseng.ac.uk

Law and Ethics in **Paediatrics**
 May 14 - 15, 2018
United Kingdom / London
 Contact: Continuing Professional Development, Imperial College London
 Phone: +44-20-7589-5111

Complex Nasal Reconstruction

May 15, 2018

United Kingdom / London

Contact: Lucy Courtney-Bennett, Organizer, Royal Society of Medicine

Phone: +44-20-7290-3945

Email: omfs@rsm.ac.uk

Multiple Pregnancy and Birth: Psychological and Clinical Issues

May 15, 2018

United Kingdom / London

Contact: Verity Cotton, Organizer, Royal Society of Medicine

Phone: +44-20-7290-3947

Email: maternity@rsm.ac.uk

11th International Congress on Autoimmunity (Autoimmunity 2018)

May 16 - 20, 2018

Portugal / Lisbon

Contact: Autoimmunity Secretariat, Kenes Group

Phone: +972-3-972-7500

Email: autoimmunity@kenes.com

2018 International Investigative Dermatology Meeting

May 16 - 19, 2018

United States / Florida / Orlando

Contact: Society for Investigative Dermatology

Phone: 216-579-9300

Email: sid@sidnet.org

2018 International Symposium on HIV & Emerging Infectious Diseases (ISHEID)

May 16 - 18, 2018

France / Marseille

Contact: Organizer, Overcome

Phone: 011-33-1-4088-9797; Fax: 011-33-1-4088-9790

Email: isheid@overcome.fr

25th International Stress & Behavior Neuroscience & Biopsychiatry Conference

May 16 - 19, 2018

Russia / St. Petersburg, Russia

Contact: Na Nutsa, Secretary, International Stress And Behavior Society (ISBS)

Phone: 240-899-9571

Email: isbs.congress@gmail.com

Paediatric Sleep

May 16 - 17, 2018

United Kingdom / London

Contact: Continuing Professional Development, Imperial College London

Phone: +44-20-7589-5111

Clinical Cases in Dermatology

May 17, 2018

United Kingdom / London

Contact: Dermatology Section, Royal Society of Medicine

Phone: +44-20-7290-3942

Email: dermatology@rsm.ac.uk

Men's & Women's Health for Primary Care

May 18 - 20, 2018

United States / California / San Diego

Contact: Medical Education Resources, Inc.

Phone: 800-421-3756 or 303-798-9682

Fax: 720-449-0217

Email: info@mer.org

Co-Morbidities in Dialysis Patients

May 21, 2018

United Kingdom / London

Contact: Verity Cotton, Organizer, Royal Society of Medicine

Phone: +44-20-7290-3947

Email: nephrology@rsm.ac.uk

2018 EuroPCR: World-Leading Course in Interventional Cardiovascular Medicine

May 22 - 25, 2018

France / Paris

Contact: PCRonline

Anaesthesia 2018: The International Meeting of the Royal College of Anaesthetists

May 22 - 23, 2018

United Kingdom / London

Contact: Royal College of Anaesthetists

Phone: +44-20-7092-1500; Fax: +44-20-7092-1730

Email: info@rcoa.ac.uk

Neurodevelopmental Disorder Prenatal Alcohol Exposure: Medical, Psychiatric and Social Consequences

May 22, 2018

United Kingdom / London

Contact: Amy Ballam, Organizer, Royal Society of Medicine

Phone: +44-20-7290-3942

Email: intellectualdisability@rsm.ac.uk

7th International Conference on Clinical Neonatology

May 23 - 26, 2018

Italy / Turin

Contact: Vittoria Paolini, Ms, MCA Scientific Events

Phone: +39-2-3493-4404

Email: paolini@mcascientificevents.eu

Explain Pain: Music, Motion and Words
 May 25, 2018
United Kingdom / London
 Contact: Daisy George, Organizer, Royal Society of
 Medicine
 Phone: +44-20-7290-2982
 Email: pain@rsm.ac.uk

Office Orthopedics & Sports Medicine for
 Primary Care
 May 25 – 27, 2018
United States / Washington / Seattle
 Contact: MCE Conferences
 Phone: 888-533-9031; Fax: 888-533-9031
 Email: info@mceconferences.com

**P4 Conference: Practical Pearls for the Primary
 Practitioner**
 May 25, 2018
United States / Pennsylvania / State College
 Contact: Continuing Education, Penn State College
 of Medicine
 Phone: 717-531-6483; Fax: 717-531-5604

**16th World Association for Infant Mental Health
 World Congress**
 May 26 - 30, 2018
Italy / Rome
 Contact: EGA Worldwide Congresses & Events
 Phone: 011-39-6-328-121
 Email: waimh2018@ega.it

**16th European Meeting on HIV & Hepatitis:
 Treatment Strategies & Antiviral Drug Resistance**
 May 30 - Jun 1, 2018
Italy / Rome
 Contact: Goda Adomonis, MA, Senior Project
 Manager, Virology Education
 Phone: +31-30-230-7147
 Email: goda.adomonis@vironet.com

Vascular Anastomosis
 May 30, 2018
United Kingdom / Glasgow
 Contact: Donna Johnston, Coordinator, Royal
 College of Physicians and Surgeons of Glasgow
 Phone: +44-14-1241-6228
 Email: donna.johnston@rcpsg.ac.uk

**2018 International Mediterranean Family Medicine
 Congress**
 Jun 1 - 3, 2018
Spain / Barcelona
 Contact: Elmas Yapici, Organizing Secretariat,
 Kumgroup Congress & Organization
 Phone: +90-5-7061-9537
 Email: organizing@imfmc.org

**Targeting Therapy of Alzheimer's and Related
 Neurodegenerative Diseases**
 Jun 1 - 4, 2018
Bahamas / Nassau
 Contact: Conference Manager, Fusion Conferences
 Phone: +44-16-3872-4137
 Email: admin@fusion-conferences.com

**35th International Society of Blood Transfusion
 International Conference / 2017 Canadian
 Society of Transfusion Medicine (CSTM) Annual
 Conference**
 Jun 2 - 6, 2018
Canada / Ontario / Toronto
 Contact: CSTM
 Phone: 855-415-3917; Fax: 866-882-7093
 Email: office@transfusion.ca

Sleep 2018
 Jun 2 - 6, 2018
United States / Maryland / Baltimore
 Contact: Associated Professional Sleep Societies
 Phone: 630-737-9700; Fax: 630-737-9789
 Email: info@sleepmeeting.org

Allergic Skin Disease
 Jun 4 - 5, 2018
United Kingdom / London
 Contact: Continuing Professional Development,
 Imperial College London
 Phone: +44-20-7589-5111

**16th World Congress on Menopause: Midlife
 Health in the 21st Century**
 Jun 6 - 9, 2018
British Columbia / Vancouver
 Contact: Ms Lee Tomkins, Executive Director,
 International Menopause Society
 Phone: 011-44-17-2688-4221
 Email: leetomkinsims@btinternet.com

Paediatric Allergy
 Jun 6 - 7, 2018
United Kingdom / London
 Contact: Continuing Professional Development,
 Imperial College London
 Phone: +44-20-7589-5111

2018 Medical Careers: The Advisor's Perspective
 Jun 7, 2018
United Kingdom / London
 Contact: Jemma Hemsworth, Organizer, Royal
 Society of Medicine
 Phone: +44-20-7290-3919
 Email: schools@rsm.ac.uk

Blended Ultrasound-Guided **Nerve Blocks** for the
Emergency Physician
Jun 8, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development
Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-4500
Email: learn@gcus.com

Singapore **Hepatology** Conference / Best of EASL
2018
Jun 8 - 9, 2018
Singapore / Singapore
Contact: Conference Manager, Singapore Hepatitis
Conference Pte Ltd
Email: info@shc-sg.com

7th Asian Conference on **Hepatitis and AIDS**
Jun 9 - 10, 2018
China / Beijing
Contact: Kun-Chieh Wu, Project Manager, Virology
Education
Phone: +31-30-230-7149
Email: kun-chief@vironet.com

9th World Congress of the World Federation of
Pediatric Intensive and Critical Care Societies
Jun 9 - 13, 2018
Singapore / Singapore
Contact: Josh Margo, Mr, Kenes Group
Phone: 011-97-2-3972-7450
Email: jmargo@kenes.com

17th Biennial Society for **Medical Decision Making**
European Conference
Jun 10 - 12, 2018
Netherlands / Leiden
Contact: Society for Medical Decision Making
Phone: 908-359-1184; Fax: 908-450-1119
Email: info@smdm.org

41st European Congress of **Cytology**
Jun 10 - 14, 2018
Spain / Madrid
Contact: Kenes Group, Kenes Group
Phone: 011-34-91-361-2600
Email: ecc2018@kenes.com

11th International Conference on **Acute Cardiac**
Care
Jun 11 - 12, 2018
Israel / Tel Aviv
Contact: Bronia Tiger, ISAS International Seminars
Phone: +972-2-652-0574; Fax: +972-2-652-0558
Email: confer@isas.co.il

Nutrition, the Immune System and Health
Jun 11, 2018
United Kingdom / London
Contact: Hatty Grant, Organizer, Royal Society of
Medicine
Phone: +44-20-7290-2984
Email: food@rsm.ac.uk

Child Health Festival: How to Advocate For
Children, Influence Policy & Change Practice
Jun 12, 2018
United Kingdom / London
Contact: Andrea Torok, Organizer, Royal Society of
Medicine
Phone: +44-20-7290-2986
Email: paediatrics@rsm.ac.uk

29th Congress of Union of the European
Phoniatricians (UEP)
Jun 13 - 16, 2018
Finland / Helsinki
Contact: Ahmed Geneid, Dr, UEP
Phone: +358-4-4330-4949
Email: ahmed.geneid@hus.fi

Sonography Principles & Instrumentation Registry
Review
Jun 13, 2018
United States / Florida / St. Petersburg
Contact: Casey Green, Business Development
Supervisor, Gulfcoast Ultrasound Institute, Inc
Phone: 727-363-4500; Fax: 727-363-0811
Email: learn@gcus.com

2nd International Conference on **Zika Virus** and
AEDS Related Infections
Jun 14 - 17, 2018
Estonia / Tallinn
Contact: Conference Secretariat, Target Conferences
Phone: +972-3-517-5150
Email: zika@target-conferences.com

5th World Congress of **Dermoscopy**
Jun 14 - 16, 2018
Greece / Thessaloniki
Contact: John Antoniou, Mr., Era Ltd
Phone: 011-30-210-363-4944; Fax: 011-30-210-363-4690
Email: jantoniou@era.gr

Specialty Skills in **Emergency Surgery and Trauma**
Jun 14 - 15, 2018
United Kingdom / Manchester
Contact: Education Team, Royal College of Surgeons
of England
Email: education@rcseng.ac.uk

Brain Injury

Jun 15, 2018

United Kingdom / London

Contact: Ruth Cloves, Organizer, Royal Society of Medicine

Phone: +44-20-7290-2985

Email: cns@rsm.ac.uk

Exercise Medicine

Jun 15, 2018

United Kingdom / London

Contact: Beilul Kahsai, Organizer, Royal Society of Medicine

Phone: +44-20-7290-3859

Email: sports@rsm.ac.uk

31st International College of**Neuropsychopharmacology (CINP) World Congress**

Jun 16 - 19, 2018

Austria / Vienna

Contact: Central Office, CINP

Phone: 011-44-13-5524-4930

Fax: 011-44-13-5524-9959

36th World **Ophthalmology** Congress of the International Council Of Ophthalmology

Jun 16 - 19, 2018

Spain / Barcelona

Contact: Secretariat, MCI Suisse Sa

Phone: 011-41-22-339-9728

Fax: 011-41-22-339-9631

Email: woc2018regshot@mci-group.com

Systematic Training in **Acute Illness** Recognition and Treatment for Surgery

Jun 16, 2018

United Kingdom / London

Contact: Education Team, Royal College of Surgeons of England

Email: education@rcseng.ac.uk

Global Contraception

Jun 19, 2018

United Kingdom / London

Contact: Amy Stratton, Organizer, Royal Society of Medicine

Phone: +44-20-7290-2980

Email: globalhealth@rsm.ac.uk

Intermediate Skills in Laparoscopic Surgery

Jun 19 - 20, 2018

United Kingdom / London

Contact: Education Team, Royal College of Surgeons of England

Email: education@rcseng.ac.uk

32nd International Computer Assisted **Radiology & Surgery (CARS) Congress & Exhibition**

Jun 20 - 23, 2018

Germany / Berlin

Contact: Mrs. Franziska Schweikert, Conference Manager, CARS Conference Office

Phone: +49-77-4292-2434

Email: office@cars-int.org

12th Asian & Oceanian **Epilepsy** Congress

Jun 21 - 24, 2018

Indonesia / Bali

Contact: Secretariat, International League against Epilepsy / International Bureau for Epilepsy

Phone: 011-353-1-205-6720

Email: bali@epilepsycongress.org

Advanced Peripheral Nerve Ultrasound:

Diagnostic & Interventional Applications

Jun 21 - 22, 2018

United States / Florida / St. Petersburg

Contact: Casey Green, Business Development Supervisor, Gulfcoast Ultrasound Institute, Inc

Phone: 727-363-4500; Fax: 727-363-0811

Email: learn@gcus.com

Cardia: Cardiac Arrhythmia, Sudden Death, Inherited **Cardiovascular Disease**, Athletes

Jun 21 - 22, 2018

United States / California / Stanford

Contact: Dianna Ziehm, CME Conference Coordinator, Stanford Health Care

Phone: 650-724-7166

Email: dziehm@stanford.edu

Clinical Cases in Dermatology

Jun 21, 2018

United Kingdom / London

Contact: Dermatology Section, Royal Society of Medicine

Phone: +44-20-7290-3942

Email: dermatology@rsm.ac.uk

Definitive Surgical Trauma Skills

Jun 21 - 22, 2018

United Kingdom / Manchester

Contact: Education Team, Royal College of Surgeons of England

Email: education@rcseng.ac.uk

14th International Regional **Stress & Behavior Neuroscience & Biopsychiatry** Conference (North America)

Jun 22 - 23, 2018

United States / Florida / Miami Beach

Contact: Na Nutsa, Secretary, International Stress And Behavior Society (ISBS)

Phone: 240-899-9571

Email: isbs.congress@gmail.com

22nd Annual **Hypertension, Diabetes and Dyslipidemia** Conference Charleston
 Jun 22 - 24, 2018
United States / South Carolina / Charleston
 Contact: Barbara Ejnes, Continuing Education Company
 Phone: 386-447-6831
 Email: barbara@cmemeeting.org

Cardio Meeting
 Jun 22, 2018
United Kingdom / London
 Contact: Emily Amos, Organizer, Royal Society of Medicine
 Phone: +44-20-7290-3935
 Email: cardiothoracic@rsm.ac.uk

2nd Annual International Congress on **Oncology Pathology™**: Towards Harmonization Of Pathology & Oncology Standards
 Jun 23, 2018
United States / New York / New York
 Contact: Physicians' Education Resource, LLC
 Phone: 609-378-3701; Fax: 609-257-0705

Innovation in **Medicine** 2018: Royal College of Physicians Annual Conference
 Jun 25 - 26, 2018
United Kingdom / London
 Contact: Royal College of Physicians
 Phone: +44-20-3075-1649

Legal Issues in **Sexuality and Sexual Health**
 Jun 26, 2018
United Kingdom / London
 Contact: Lucy Courtney-Bennett, Organizer, Royal Society of Medicine
 Phone: +44-20-7290-3945
 Email: sexmed@rsm.ac.uk

Musculoskeletal Ultrasound in **Hemophilia**
 Jun 27 - 29, 2018
United States / California / San Diego
 Contact: Marlene Zepeda, Continuing Medical Education, UC San Diego
 Phone: 858-534-3940
 Email: ocme@ucsd.edu

2018 Asia Pacific **AIDS & Co-Infections** Conference
 Jun 28 - 30, 2018
China / Hong Kong
 Contact: Virology Education
 Phone: +31-30-230-7142

2018 **Pulmonary Hypertension** Association (PHA) International Pulmonary Hypertension Conference & Scientific Sessions
 Jun 29 - Jul 1, 2018
United States / Florida / Orlando
 Contact: PHA
 Phone: 301-565-3004; Fax: 301-565-3994
 Email: pha@phassociation.org

The Traveller: **Infectious and Tropical Diseases**
 Jun 29, 2018
United Kingdom / London
 Contact: Emergency Medicine Section, Royal Society of Medicine
 Phone: +44-20-7290-3935
 Email: emergency@rsm.ac.uk

25th Biennial Congress of the European Association for **Cancer** Research (EACR)
 Jun 30 - Jul 3, 2018
Netherlands / Amsterdam
 Contact: Kathryn Wass, Office and Conference Series Manager, EACR
 Phone: 011-44-11-5951-5114
 Email: kathryn.wass@nottingham.ac.uk

Patient Safety, Drug Abuse, Psychiatry & **Pharmacogenomics**
 Jun 30 - Jul 7, 2018
United States / Washington / Seattle
 Contact: University Learning Systems
 Phone: 800-940-5860; Fax: 716-529-0550
 Email: info@universitylearning.com

18th European Congress on **Biotechnology**
 Jul 1 - 4, 2018
Switzerland / Geneva
 Contact: Congress Team, TFI Group
 Phone: 011-44-20-7808-5171
 Email: ecb2018@tfigroup.com

Child Public Health and Social **Paediatrics**
 Jul 2 - 3, 2018
United Kingdom / London
 Contact: Continuing Professional Development, Imperial College London
 Phone: +44-20-7589-5111

Dementia and Radiology
 Jul 5, 2018
United Kingdom / London
 Contact: Emily Amos, Organizer, Royal Society of Medicine
 Phone: +44-20-7290-3937
 Email: radiology@rsm.ac.uk

5th International Congress on Naturopathic Medicine

Jul 6 - 8, 2018

United Kingdom / London

Contact: Conference Secretariat, International Congress on Naturopathic Medicine

Phone: +44-17-4582-8400

Email: secretariat@icnmnaturopathy.eu

2018 Federation of European Neurosciences Societies Forum

Jul 7 - 11, 2018

Germany / Berlin

Contact: Ron Marcovici, Mr., Kenes Group

Phone: 011-41-2-2908-0488

Email: rmarcovici@kenes.com

Hypnosis in Practice & Theory – Towards a Synthesis of Academic & Clinical Protocols

Jul 7 - 8, 2018

United Kingdom / London

Contact: Verity Cotton, Organizer, Royal Society of Medicine

Phone: +44-20-7290-3947

Email: hypnosis@rsm.ac.uk

47th Annual Scientific Meeting of the Society for Academic Primary Care

Jul 10 - 12, 2018

United Kingdom / London

Contact: Secretariat, Society for Academic Primary Care

Phone: +44-18-6533-1839

Email: office@sapc.ac.uk

25th International Meeting on Advanced Spine Techniques

Jul 11 - 14, 2018

United States / California / Los Angeles

Contact: Scoliosis Research Society

Phone: 414-289-9107; Fax: 414-276-3349

Email: info@srs.org

13th Annual Scientific Meeting of the Society of Cardiovascular Computed Tomography

Jul 12 - 15, 2018

United States / Texas / Grapevine

Contact: Society of Cardiovascular Computed Tomography

Phone: 800-876-4195 or 703-766-1706

Email: info@scct.org

10th Annual International Workshop on HIV Pediatrics

Jul 20 - 21, 2018

Netherlands / Amsterdam

Contact: Virology Education

Phone: +31-30-230-7142

Email: info@virology-education.com

6th Scientific Meeting of the World Society for Pediatric & Congenital Heart Surgery / 18th International Symposium on Congenital Heart Disease

Jul 22 - 26, 2018

United States / Florida / Orlando

Contact: Suzanne Anderson, Conference Coordinator, Johns Hopkins All Children's Hospital

Phone: 727-767-2565; Fax: 727-767-8601

Email: suzanne.anderson@jhmi.edu

Diabetes Asia 2018 Conference

Jul 26 - 29, 2018

Malaysia / Kuching

Contact: Suaidah, Ms., National Diabetes Institute (NADI) Malaysia

Phone: +60-3-7876-1676; Fax: +60-3-7876-1679

Email: suaidah.nadi16@gmail.com

31st Annual In Vitro Fertilization & Embryo Transfer

Jul 30 - Aug, 2018

United States / California / San Diego

Contact: Bermelilyn Imamura, Continuing Medical Education, UC San Diego

Phone: 858-534-3940

Email: ocme@ucsd.edu

14th Global Conference on Ageing

Aug 8 - 10, 2018

Canada / Ontario / Toronto

Contact: Ms. Savanah Duchen, Events Management Officer, International Federation on Ageing

Phone: 416-342-1655

Email: sduchen@ifa-fiv.org

23rd Annual Challenges in Critical Care: A Multidisciplinary Approach

Aug 24, 2018

United States / Pennsylvania / Hershey

Contact: Continuing Education, Penn State College of Medicine

Phone: 717-531-6483; Fax: 717-531-5604

14th International Congress of Neuroimmunology / 2nd Global Schools of Neuroimmunology Pre-Course

Aug 27 - 31, 2018

Australia / Brisbane

Contact: Secretariat, International Society of Neuroimmunology

Fax: 011-39-6-519-4009

Email: secretariat@isniweb.org

WHO-Facts Sheet

1. Climate change and health
2. Deafness and hearing loss
3. Food additives
4. Headache disorders
5. Leprosy

Compiled and edited by
Vineetha E Mammen

Kuwait Medical Journal 2018; 50 (1): 133 - 142

1. CLIMATE CHANGE AND HEALTH

Over the last 50 years, human activities – particularly the burning of fossil fuels – have released sufficient quantities of carbon dioxide and other greenhouse gases to trap additional heat in the lower atmosphere and affect the global climate.

In the last 130 years, the world has warmed by approximately 0.85°C. Each of the last 3 decades has been successively warmer than any preceding decade since 1850(1).

Sea levels are rising, glaciers are melting and precipitation patterns are changing. Extreme weather events are becoming more intense and frequent.

Key facts

- Climate change affects the social and environmental determinants of health – clean air, safe drinking water, sufficient food and secure shelter.
- Between 2030 and 2050, climate change is expected to cause approximately 250 000 additional deaths per year, from malnutrition, malaria, diarrhoea and heat stress.
- The direct damage costs to health (i.e. excluding costs in health-determining sectors such as agriculture and water and sanitation), is estimated to be between US\$ 2-4 billion/year by 2030.
- Areas with weak health infrastructure – mostly in developing countries – will be the least able to cope without assistance to prepare and respond.
- Reducing emissions of greenhouse gases through better transport, food and energy-use choices can result in improved health, particularly through reduced air pollution.

What is the impact of climate change on health?

Although global warming may bring some localized benefits, such as fewer winter deaths in temperate climates and increased food production in certain areas, the overall health effects of a changing climate are likely to be overwhelmingly negative. Climate change affects social and environmental determinants of health – clean air, safe drinking water, sufficient food and secure shelter.

Extreme heat

Extreme high air temperatures contribute directly to deaths from cardiovascular and respiratory disease, particularly among elderly people. In the heat wave of summer 2003 in Europe for example, more than 70 000 excess deaths were recorded(2).

High temperatures also raise the levels of ozone and other pollutants in the air that exacerbate cardiovascular and respiratory disease.

Pollen and other aeroallergen levels are also higher in extreme heat. These can trigger asthma, which affects around 300 million people. Ongoing temperature increases are expected to increase this burden.

Natural disasters and variable rainfall patterns

Globally, the number of reported weather-related natural disasters has more than tripled since the 1960s. Every year, these disasters result in over 60 000 deaths, mainly in developing countries.

Rising sea levels and increasingly extreme weather events will destroy homes, medical facilities and other essential services. More than half of the world's population lives within 60 km of the sea. People may be forced to move, which in turn heightens the risk

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of a range of health effects, from mental disorders to communicable diseases.

Increasingly variable rainfall patterns are likely to affect the supply of fresh water. A lack of safe water can compromise hygiene and increase the risk of diarrhoeal disease, which kills over 500 000 children aged under 5 years, every year. In extreme cases, water scarcity leads to drought and famine. By the late 21st century, climate change is likely to increase the frequency and intensity of drought at regional and global scale(1).

Floods are also increasing in frequency and intensity, and the frequency and intensity of extreme precipitation is expected to continue to increase throughout the current century(1). Floods contaminate freshwater supplies, heighten the risk of water-borne diseases, and create breeding grounds for disease-carrying insects such as mosquitoes. They also cause drownings and physical injuries, damage homes and disrupt the supply of medical and health services.

Rising temperatures and variable precipitation are likely to decrease the production of staple foods in many of the poorest regions. This will increase the prevalence of malnutrition and undernutrition, which currently cause 3.1 million deaths every year.

Patterns of infection

Climatic conditions strongly affect water-borne diseases and diseases transmitted through insects, snails or other cold blooded animals.

Changes in climate are likely to lengthen the transmission seasons of important vector-borne diseases and to alter their geographic range. For example, climate change is projected to widen significantly the area of China where the snail-borne disease schistosomiasis occurs(3).

Malaria is strongly influenced by climate. Transmitted by *Anopheles* mosquitoes, malaria kills over 400 000 people every year – mainly African children under 5 years old. The *Aedes* mosquito vector of dengue is also highly sensitive to climate conditions, and studies suggest that climate change is likely to continue to increase exposure to dengue.

Measuring the health effects

Measuring the health effects from climate change can only be very approximate. Nevertheless, a WHO assessment, taking into account only a subset of the possible health impacts, and assuming continued economic growth and health progress, concluded that climate change is expected to cause approximately 250 000 additional deaths per year between 2030 and 2050; 38 000 due to heat exposure in elderly people, 48 000 due to diarrhoea, 60 000 due to malaria, and 95 000 due to childhood under-nutrition.

Who is at risk?

All populations will be affected by climate change, but some are more vulnerable than others. People living in small island developing states and other coastal regions, megacities, and mountainous and polar regions are particularly vulnerable.

Children – in particular, children living in poor countries – are among the most vulnerable to the resulting health risks and will be exposed longer to the health consequences. The health effects are also expected to be more severe for elderly people and people with infirmities or pre-existing medical conditions.

Areas with weak health infrastructure – mostly in developing countries – will be the least able to cope without assistance to prepare and respond.

WHO response

Many policies and individual choices have the potential to reduce greenhouse gas emissions and produce major health co-benefits. For example, cleaner energy systems, and promoting the safe use of public transportation and active movement – such as cycling or walking as alternatives to using private vehicles – could reduce carbon emissions, and cut the burden of household air pollution, which causes some 4.3 million deaths per year, and ambient air pollution, which causes about 3 million deaths every year.

In 2015, the WHO Executive Board endorsed a new work plan on climate change and health. This includes:

- **Partnerships:** to coordinate with partner agencies within the UN system, and ensure that health is properly represented in the climate change agenda.
- **Awareness raising:** to provide and disseminate information on the threats that climate change presents to human health, and opportunities to promote health while cutting carbon emissions.
- **Science and evidence:** to coordinate reviews of the scientific evidence on the links between climate change and health, and develop a global research agenda.
- **Support for implementation of the public health response to climate change:** to assist countries to build capacity to reduce health vulnerability to climate change, and promote health while reducing carbon emissions.

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1. IPCC, 2014: Summary for Policymakers. In: Climate Change 2014: Mitigation of Climate Change. Contribution of Working Group III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Edenhofer, O., R. Pichs-Madruga, Y. Sokona, E. Farahani, S. Kadner, K. Seyboth, A. Adler,

- I. Baum, S. Brunner, P. Eickemeier, B. Kriemann, J. Savolainen, S. Schlömer, C. von Stechow, T. Zwickel and J.C. Minx (eds.]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA.
2. Death toll exceeded 70,000 in Europe during the summer of 2003. Robine JM, Cheung SL, Le Roy S, Van Oyen H, Griffiths C, Michel JP, et al. *C R Biol.* 2008;331(2):171-8.
 3. Potential impact of climate change on schistosomiasis transmission in China. Zhou XN, Yang GJ, Yang K, Wang XH, Hong QB, Sun LP, et al. *Am J Trop Med Hyg.* 2008;78(2):188-94.

2. DEAFNESS AND HEARING LOSS

Over 5% of the world's population – 360 million people – has disabling hearing loss (328 million adults and 32 million children). Disabling hearing loss refers to hearing loss greater than 40 decibels (dB) in the better hearing ear in adults and a hearing loss greater than 30 dB in the better hearing ear in children. The majority of people with disabling hearing loss live in low- and middle-income countries.

Approximately one third of people over 65 years of age are affected by disabling hearing loss. The prevalence in this age group is greatest in South Asia, Asia Pacific and sub-Saharan Africa.

Key facts

- 360 million people worldwide have disabling hearing loss (1), and 32 million of these are children.
- Hearing loss may result from genetic causes, complications at birth, certain infectious diseases, chronic ear infections, the use of particular drugs, exposure to excessive noise, and ageing.
- 60% of childhood hearing loss is due to preventable causes.
- 1.1 billion young people (aged between 12–35 years) are at risk of hearing loss due to exposure to noise in recreational settings.
- Unaddressed hearing loss poses an annual global cost of 750 billion international dollars (2). Interventions to prevent, identify and address hearing loss are cost-effective and can bring great benefit to individuals.
- People with hearing loss benefit from early identification; use of hearing aids, cochlear implants and other assistive devices; captioning and sign language; and other forms of educational and social support.

Hearing loss and deafness

A person who is not able to hear as well as someone with normal hearing – hearing thresholds of 25 dB or better in both ears – is said to have hearing loss. Hearing loss may be mild, moderate, severe, or profound. It can

affect one ear or both ears, and leads to difficulty in hearing conversational speech or loud sounds.

'Hard of hearing' refers to people with hearing loss ranging from mild to severe. People who are hard of hearing usually communicate through spoken language and can benefit from hearing aids, cochlear implants, and other assistive devices as well as captioning. People with more significant hearing losses may benefit from cochlear implants.

'Deaf' people mostly have profound hearing loss, which implies very little or no hearing. They often use sign language for communication.

Causes of hearing loss and deafness

The causes of hearing loss and deafness can be divided into congenital causes and acquired causes.

Congenital causes

Congenital causes may lead to hearing loss being present at or acquired soon after birth. Hearing loss can be caused by hereditary and non-hereditary genetic factors or by certain complications during pregnancy and childbirth, including:

- maternal rubella, syphilis or certain other infections during pregnancy;
- low birth weight;
- birth asphyxia (a lack of oxygen at the time of birth);
- inappropriate use of particular drugs during pregnancy, such as aminoglycosides, cytotoxic drugs, antimalarial drugs, and diuretics;
- severe jaundice in the neonatal period, which can damage the hearing nerve in a newborn infant.

Acquired causes

Acquired causes may lead to hearing loss at any age, such as:

- infectious diseases including meningitis, measles and mumps;
- chronic ear infections;
- collection of fluid in the ear (otitis media);
- use of certain medicines, such as those used in the treatment of neonatal infections, malaria, drug-resistant tuberculosis, and cancers;
- injury to the head or ear;
- excessive noise, including occupational noise such as that from machinery and explosions;
- recreational exposure to loud sounds such as that from use of personal audio devices at high volumes and for prolonged periods of time and regular attendance at concerts, nightclubs, bars and sporting events;
- ageing, in particular due to degeneration of sensory cells; and
- wax or foreign bodies blocking the ear canal.

Among children, chronic otitis media is a common cause of hearing loss.

Impact of hearing loss

Functional impact

One of the main impacts of hearing loss is on the individual's ability to communicate with others. Spoken language development is often delayed in children with unaddressed hearing loss.

Unaddressed hearing loss and ear diseases such as otitis media can have a significantly adverse effect on the academic performance of children. They often have increased rates of grade failure and greater need for education assistance. Access to suitable accommodations is important for optimal learning experiences but are not always available.

Social and emotional impact

Exclusion from communication can have a significant impact on everyday life, causing feelings of loneliness, isolation, and frustration, particularly among older people with hearing loss.

Economic impact

WHO estimates that unaddressed hearing loss poses an annual global cost of 750 billion international dollars. This includes health sector costs (excluding the cost of hearing devices), costs of educational support, loss of productivity, and societal costs.

In developing countries, children with hearing loss and deafness rarely receive any schooling. Adults with hearing loss also have a much higher unemployment rate. Among those who are employed, a higher percentage of people with hearing loss are in the lower grades of employment compared with the general workforce.

Improving access to education and vocational rehabilitation services, and raising awareness especially among employers about the needs of people with hearing loss, will decrease unemployment rates for people with hearing loss.

Prevention

Overall, it is suggested that half of all cases of hearing loss can be prevented through public health measures.

In children under 15 years of age, 60% of hearing loss is attributable to preventable causes. This figure is higher in low- and middle-income countries (75%) as compared to high-income countries (49%). Overall, preventable causes of childhood hearing loss include:

- Infections such as mumps, measles, rubella, meningitis, cytomegalovirus infections, and chronic otitis media (31%).
- Complications at the time of birth, such as birth

asphyxia, low birth weight, prematurity, and jaundice (17%).

- Use of ototoxic medicines in expecting mothers and babies (4%).
- Others (8%)

Some simple strategies for prevention of hearing loss include:

- immunizing children against childhood diseases, including measles, meningitis, rubella and mumps;
- immunizing adolescent girls and women of reproductive age against rubella before pregnancy;
- preventing cytomegalovirus infections in expectant mothers through good hygiene; screening for and treating syphilis and other infections in pregnant women;
- strengthening maternal and child health programmes, including promotion of safe childbirth;
- following healthy ear care practices;
- screening of children for otitis media, followed by appropriate medical or surgical interventions;
- avoiding the use of particular drugs which may be harmful to hearing, unless prescribed and monitored by a qualified physician;
- referring infants at high risk, such as those with a family history of deafness or those born with low birth weight, birth asphyxia, jaundice or meningitis, for early assessment of hearing, to ensure prompt diagnosis and appropriate management, as required;
- reducing exposure (both occupational and recreational) to loud sounds by raising awareness about the risks; developing and enforcing relevant legislation; and encouraging individuals to use personal protective devices such as earplugs and noise-cancelling earphones and headphones.

Identification and management

Early detection and intervention are crucial to minimizing the impact of hearing loss on a child's development and educational achievements. In infants and young children with hearing loss, early identification and management through infant hearing screening programmes can improve the linguistic and educational outcomes for the child. Children with deafness should be given the opportunity to learn sign language along with their families.

Pre-school, school and occupational screening for ear diseases and hearing loss is an effective tool for early identification and management of hearing loss.

People with hearing loss can benefit from the use of hearing devices, such as hearing aids, cochlear implants, and other assistive devices. They may also benefit from speech therapy, aural rehabilitation and other related services. However, global production of

hearing aids meets less than 10% of global need and less than 3% of developing countries' needs. The lack of availability of services for fitting and maintaining these devices, and the lack of batteries are also barriers in many low-income settings.

Making properly-fitted, affordable hearing aids and cochlear implants and providing accessible follow-up services in all parts of the world will benefit many people with hearing loss.

People who develop hearing loss can learn to communicate through development of lip-reading skills, use of written or printed text, and sign language. Teaching in sign language will benefit children with hearing loss, while provision of captioning and sign language interpretation on television will facilitate access to information.

Officially recognizing national sign languages and increasing the availability of sign language interpreters are important actions to improve access to sign language services. Encouraging organizations of people with hearing loss, parents and family support groups; and strengthening human rights legislation can also help ensure better inclusion for people with hearing loss.

WHO response

WHO assists Member States in developing programmes for ear and hearing care that are integrated into the primary health-care system of the country. WHO's work includes:

- providing technical support to Member States in development and implementation of national plans for hearing care;
- providing technical resources and guidance for training of health-care workers on hearing care;
- developing and disseminating recommendations to address the major preventable causes of hearing loss;
- undertaking advocacy to raise awareness about the prevalence, causes and impact of hearing loss as well as opportunities for prevention, identification and management;
- developing and disseminating evidence-based tools for effective advocacy;
- observing and promoting World Hearing Day as an annual advocacy event;
- building partnerships to develop strong hearing care programmes, including initiatives for affordable hearing aids, cochlear implants and services;
- collating data on deafness and hearing loss to demonstrate the scale and the impact of the problem;
- promoting safe listening to reduce the risk of recreational noise-induced hearing loss through

the WHO Make Listening Safe initiative; and

- promoting social inclusion of people with disabilities, including people with hearing loss and deafness, for example, through community-based rehabilitation networks and programmes.
1. Disabling hearing loss refers to hearing loss greater than 40dB in the better hearing ear in adults and a hearing loss greater than 30dB in the better hearing ear in children.
 2. An international dollar is a currency unit defined by the World Bank.

3. FOOD ADDITIVES

Key facts

- Food additives are substances added to food to maintain or improve its safety, freshness, taste, texture, or appearance.
- Food additives need to be checked for potential harmful effects on human health before they can be used.
- The Joint FAO/WHO Expert Committee on Food Additives (JECFA), is the international body responsible for evaluating the safety of food additives.
- Only food additives that have been evaluated and deemed safe by JECFA, on the basis of which maximum use levels have been established by the Codex Alimentarius Commission, can be used in foods that are traded internationally.

What are food additives?

Substances that are added to food to maintain or improve the safety, freshness, taste, texture, or appearance of food are known as food additives. Some food additives have been in use for centuries for preservation – such as salt (in meats such as bacon or dried fish), sugar (in marmalade), or sulfur dioxide (in wine).

Many different food additives have been developed over time to meet the needs of food production, as making food on a large scale is very different from making them on a small scale at home. Additives are needed to ensure processed food remains safe and in good condition throughout its journey from factories or industrial kitchens, during transportation to warehouses and shops, and finally to consumers.

The use of food additives is only justified when their use has a technological need, does not mislead consumers, and serves a well-defined technological function, such as to preserve the nutritional quality of the food or enhance the stability of the food.

Food additives can be derived from plants, animals, or minerals, or they can be synthetic. They are added intentionally to food to perform certain technological purposes which consumers often take for granted. There are several thousand food additives used, all of which are designed to do a specific job in making food safer or more appealing. WHO, together with FAO, groups food additives into 3 broad categories based on their function.

Flavouring agents

Flavouring agents – which are added to food to improve aroma or taste – make up the greatest number of additives used in foods. There are hundreds of varieties of flavourings used in a wide variety of foods, from confectionery and soft drinks to cereal, cake, and yoghurt. Natural flavouring agents include nut, fruit and spice blends, as well as those derived from vegetables and wine. In addition, there are flavourings that imitate natural flavours.

Enzyme preparations

Enzyme preparations are a type of additive that may or may not end up in the final food product. Enzymes are naturally-occurring proteins that boost biochemical reactions by breaking down larger molecules into their smaller building blocks. They can be obtained by extraction from plants or animal products or from micro-organisms such as bacteria and are used as alternatives to chemical-based technology. They are mainly used in baking (to improve the dough), for manufacturing fruit juices (to increase yields), in wine making and brewing (to improve fermentation), as well as in cheese manufacturing (to improve curd formation).

Other additives

Other food additives are used for a variety of reasons, such as preservation, colouring, and sweetening. They are added when food is prepared, packaged, transported, or stored, and they eventually become a component of the food.

Preservatives can slow decomposition caused by mould, air, bacteria, or yeast. In addition to maintaining the quality of the food, preservatives help control contamination that can cause foodborne illness, including life-threatening botulism.

Colouring is added to food to replace colours lost during preparation, or to make food look more attractive.

Non-sugar sweeteners are often used as an alternative to sugar because they contribute fewer or no calories when added to food.

WHO response

Evaluating the health risk of food additives

WHO, in cooperation with the Food and Agriculture Organization of the United Nations (FAO), is responsible for assessing the risks to human health from food additives. Risk assessment of food additives are conducted by an independent, international expert scientific group – the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

Only food additives that have undergone a JECFA safety assessment, and are found not to present an appreciable health risk to consumers, can be used. This applies whether food additives come from a natural source or they are synthetic. National authorities, either based on the JECFA assessment or a national assessment, can then authorize the use of food additives at specified levels for specific foods.

JECFA evaluations are based on scientific reviews of all available biochemical, toxicological, and other relevant data on a given additive – mandatory tests in animals, research studies and observations in humans are considered. The toxicological tests required by JECFA include acute, short-term, and long-term studies that determine how the food additive is absorbed, distributed, and excreted, and possible harmful effects of the additive or its by-products at certain exposure levels.

The starting point for determining whether a food additive can be used without having harmful effects is to establish the acceptable daily intake (ADI). The ADI is an estimate of the amount of an additive in food or drinking water that can be safely consumed daily over a lifetime without adverse health effects.

International standards for the safe use of food additives

The safety assessments completed by JECFA are used by the joint intergovernmental food standard-setting body of FAO and WHO, the Codex Alimentarius Commission, to establish levels for maximum use of additives in food and drinks. Codex standards are the reference for national standards for consumer protection, and for the international trade in food, so that consumers everywhere can be confident that the food they eat meets the agreed standards for safety and quality, no matter where it was produced.

Once a food additive has been found to be safe for use by JECFA and maximum use levels have been established in the Codex General Standard for Food Additives, national food regulations need to be implemented permitting the actual use of a food additive.

How do I know which additives are in my food?

The Codex Alimentarius Commission also

establishes standards and guidelines on food labelling. These standards are implemented in most countries, and food manufacturers are obliged to indicate which additives are in their products. In the European Union, for example, there is legislation governing labelling of food additives according to a set of pre-defined "E-numbers". People who have allergies or sensitivities to certain food additives should check labels carefully.

WHO encourages national authorities to monitor and ensure that food additives in food and drinks produced in their countries comply with permitted uses, conditions and legislation. National authorities should oversee the food business, which carries the primary responsibility for ensuring that the use of a food additive is safe and complies with legislation.

4. HEADACHE DISORDERS

Key facts

- Headache disorders are among the most common disorders of the nervous system.
- It has been estimated that almost half of the adult population have had a headache at least once within the last year.
- Headache disorders, which are characterized by recurrent headache, are associated with personal and societal burdens of pain, disability, damaged quality of life, and financial cost.
- Worldwide, a minority of people with headache disorders are diagnosed appropriately by a health-care provider.
- Headache has been underestimated, under-recognized and under-treated throughout the world.

What are headache disorders?

Headache disorders, characterized by recurrent headache, are among the most common disorders of the nervous system. Headache itself is a painful and disabling feature of a small number of primary headache disorders, namely migraine, tension-type headache, and cluster headache. Headache can also be caused by or occur secondarily to a long list of other conditions, the most common of which is medication-overuse headache.

How common are headache disorders?

Globally, it has been estimated that prevalence among adults of current headache disorder (symptomatic at least once within the last year) is about 50%. Half to three quarters of adults aged 18–65 years in the world have had headache in the last year and, among those individuals, 30% or more have reported migraine. Headache on 15 or more days every

month affects 1.7–4% of the world's adult population. Despite regional variations, headache disorders are a worldwide problem, affecting people of all ages, races, income levels and geographical areas.

What is the burden due to headache disorders?

Not only is headache painful, but it is also disabling. In the Global Burden of Disease Study, updated in 2013, migraine on its own was found to be the sixth highest cause worldwide of years lost due to disability (YLD). Headache disorders collectively were third highest.

Headache disorders impose a recognizable burden on sufferers including sometimes substantial personal suffering, impaired quality of life and financial cost. Repeated headache attacks, and often the constant fear of the next one, damage family life, social life and employment. The long-term effort of coping with a chronic headache disorder may also predispose the individual to other illnesses. For example, anxiety and depression are significantly more common in people with migraine than in healthy individuals.

Types of headache disorders

Migraine, tension-type headache and medication-overuse headache are of public health importance since they are responsible for high population levels of disability and ill-health.

Migraine

- A primary headache disorder.
- Migraine most often begins at puberty and most affects those aged between 35 and 45 years.
- It is more common in women, usually by a factor of about 2:1, because of hormonal influences.
- It is caused by the activation of a mechanism deep in the brain that leads to release of pain-producing inflammatory substances around the nerves and blood vessels of the head.
- Migraine is recurrent, often life-long, and characterized by recurring attacks.
- Attacks typically include:
 - o headache, which is:
 - § of moderate or severe intensity
 - § one-sided
 - § pulsating in quality
 - § aggravated by routine physical activity
 - § with duration of hours to 2-3 days
 - o nausea (the most characteristic associated feature);
 - o attack frequency is anywhere between once a year and once a week; and
 - o in children, attacks tend to be of shorter duration and abdominal symptoms more prominent.

Tension-type headache (TTH)

- TTH is the most common primary headache disorder.
- Episodic TTH, occurring on fewer than 15 days per month, is reported by more than 70% of some populations.
- Chronic TTH, occurring on more than 15 days per month, affects 1-3% of adults.
- TTH often begins during the teenage years, affecting three women to every two men.
- Its mechanism may be stress-related or associated with musculoskeletal problems in the neck.
- Episodic TTH attacks usually last a few hours, but can persist for several days.
- Chronic TTH can be unremitting and is much more disabling than episodic TTH.
- This headache is described as pressure or tightness, often like a band around the head, sometimes spreading into or from the neck.

Cluster Headache (CH)

- A primary headache disorder.
- CH is relatively uncommon affecting fewer than 1 in 1000 adults, affecting six men to each woman.
- Most people developing CH are in their 20s or older.
- It is characterized by frequently recurring (up to several times a day), brief but extremely severe headache, usually focused in or around one eye, with tearing and redness of the eye, the nose runs or is blocked on the affected side and the eyelid may droop.
- CH has episodic and chronic forms.

Medication-overuse headache (MOH)

- MOH is caused by chronic and excessive use of medication to treat headache.
- MOH is the most common secondary headache disorder.
- It may affect up to 5% of some populations, women more than men.
- MOH occurs by definition on more days than not, is oppressive, persistent and often at its worst on awakening.

Social and economic burden of headache

Headache disorders are a public-health concern given the associated disability and financial costs to society. As headache disorders are most troublesome in the productive years (late teens to 50s), estimates of their financial cost to society – principally from lost working hours and reduced productivity – are massive. In the United Kingdom, for example, some 25 million working- or school-days are lost every year because of

migraine alone; this financial cost may be matched by TTH and MOH combined. Headache is high among causes of consulting medical practitioners: one-third of all neurological consultations were for headache, in one survey.

Yet, many of those troubled by headache do not receive effective care. For example, in the United States of America and the United Kingdom, only half of those identified with migraine had seen a doctor for headache-related reasons in the previous 12 months, and only two-thirds had been correctly diagnosed. Most were solely reliant on over-the-counter medications.

Treatment

Appropriate treatment of headache disorders requires training of health professionals, accurate diagnosis and recognition of the conditions, appropriate treatment with cost-effective medications, simple lifestyle modifications, and patient education. The main classes of drugs to treat headache disorders include: analgesics, anti-emetics, specific anti-migraine medications, and prophylactic medications.

Barriers to effective care

Lack of knowledge among health-care providers is the principal clinical barrier. Worldwide, on average, only 4 hours of undergraduate medical education are dedicated to instruction on headache disorders. A large number of people with headache disorders are not diagnosed and treated: worldwide only 40% of those with migraine or TTH are professionally diagnosed, and only 10% of those with MOH.

Poor awareness extends to the general public. Headache disorders are not perceived by the public as serious since they are mostly episodic, do not cause death, and are not contagious. The low consultation rates in developed countries may indicate that many affected people are unaware that effective treatments exist. Half of people with headache disorders are estimated to be self-treating.

Many governments, seeking to constrain health-care costs, do not acknowledge the substantial burden of headache on society. They might not recognize that the direct costs of treating headache are small in comparison with the huge indirect-cost savings that might be made (eg, by reducing lost working days) if resources were allocated to treat headache disorders appropriately.

WHO response

These evident burdens call for action. WHO recognizes this, and is a partner, with the non-governmental organization Lifting The Burden,

in the Global Campaign against Headache. This initiative commenced in 2004 and aims not only to raise awareness of headache disorders but also to improve the quality of headache care and access to it worldwide. WHO published the Atlas of headache disorders in 2011, describing the burden due to headache disorders and resources available to reduce them.

5. LEPROSY

Key facts

- Leprosy is a chronic disease caused by a bacillus, *Mycobacterium leprae*.
- *M. leprae* multiplies slowly and the incubation period of the disease, on average, is 5 years. In some cases, symptoms may occur within 1 year but can also take as long as 20 years to occur.
- The disease mainly affects the skin, the peripheral nerves, mucosa of the upper respiratory tract, and also the eyes.
- Leprosy is curable with multidrug therapy (MDT).
- Leprosy is transmitted via droplets, from the nose and mouth, during close and frequent contacts with untreated cases.
- Untreated, leprosy can cause progressive and permanent damage to the skin, nerves, limbs, and eyes.
- There were 216 108 new leprosy cases registered globally in 2016, according to official figures from 145 countries from the 6 WHO Regions.
- Based on 173 358 cases at the end of 2016, prevalence rate corresponds to 0.29/10,000.

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, an acid-fast, rod-shaped bacillus. The disease mainly affects the skin, the peripheral nerves, mucosa of the upper respiratory tract, and the eyes. Leprosy is curable and treatment in the early stages can prevent disability.

Brief history of the disease and treatment

Leprosy is an age-old disease, described in the literature of ancient civilizations. Throughout history, people afflicted have often been ostracized by their communities and families.

Although leprosy was managed differently in the past, the first breakthrough occurred in the 1940s with the development of the medicine dapsone. The duration of treatment lasted many years, often a lifetime, making compliance difficult. In the 1960s, *M. leprae* started to develop resistance

to dapsone, the world's only known anti-leprosy medicine at that time. In the early 1960s, rifampicin and Clofazimine were discovered and subsequently added to the treatment regimen, which was later labelled as multidrug therapy (MDT).

In 1981, a WHO Study Group recommended MDT. MDT consists of 2 or 3 medicines: dapsone and rifampicin for all patients, with Clofazimine added for multi-bacillary disease. This latter combination kills the pathogen and cures the patient.

Since 1995 WHO has provided MDT free of cost to all leprosy patients in the world. Free MDT was initially funded by The Nippon Foundation, and since 2000 it is donated through an agreement with Novartis. This donation runs until 2020.

Elimination of leprosy as public health problem (defined as a registered prevalence of less than 1 case per 10 000 population) was achieved globally in 2000. More than 16 million leprosy patients have been treated with MDT over the past 20 years.

WHO response

In 2016 WHO launched its "Global Leprosy Strategy 2016–2020: Accelerating towards a leprosy-free world" to reinvigorate efforts for leprosy control. The strategy focuses on avoiding disabilities, especially among children.

- The Global Leprosy Strategy 2016–2020: Accelerating towards a leprosy-free world
- The *Global Leprosy Strategy 2016–2020* is structured around following 3 core pillars:

Pillar I: Strengthen government ownership, coordination and partnership

Key interventions

- Ensuring political commitment and adequate resources for leprosy programmes.
- Contributing to universal health coverage with a special focus on children, women and underserved populations including migrants and displaced people.
- Promoting partnerships with state and non-state actors and promoting intersectoral collaboration and partnerships at the international and national levels.
- Facilitating and conducting basic and operational research in all aspects of leprosy and maximizing the evidence base to inform policies, strategies and activities.
- Strengthening surveillance and health information systems for programme monitoring and evaluation (including geographical information systems).

Pillar II: Stop leprosy and its complications

Key interventions

- Strengthening patient and community awareness of leprosy.
- Promoting early case detection through active case-finding (such as campaigns) in areas of higher endemicity and contact management.
- Ensuring prompt start of, and adherence to treatment, including working towards improved treatment regimens.
- Improving prevention and management of disabilities.
- Strengthening surveillance for antimicrobial resistance including laboratory network.
- Promoting innovative approaches for training, referrals, and sustaining expertise in leprosy, such as e-health.
- Promoting interventions for the prevention of infection and disease.

Pillar III: Stop discrimination and promote inclusion

Key interventions

- Promoting societal inclusion by addressing all forms of discrimination and stigma.
- Empowering persons affected by leprosy and strengthening their capacity to participate actively in leprosy services.
- Involving communities in action for improvement of leprosy services.
- Promoting coalition-building among persons affected by leprosy and encouraging the integration of these coalitions and/or their members with other community-based organizations.

- Promoting access to social and financial support services, for example to facilitate income generation, for persons affected by leprosy and their families.
- Supporting community-based rehabilitation for people with leprosy-related disabilities.
- Working towards abolishing discriminatory laws and promoting policies facilitating inclusion of persons affected by leprosy.

Targets of the Global Leprosy Strategy

- Zero disabilities among new paediatric patients.
- A grade-2 disability rate of less than 1 case per 1 million people.
- Zero countries with legislation allowing discrimination on basis of leprosy.

In August 2016, WHO published an Operational Manual to facilitate adaptation and implementation of the *Global Leprosy Strategy 2016–2020*. The manual provides guidance for managers of national leprosy programmes (or equivalent entities) to adapt and implement the Global Leprosy Strategy according to the epidemiological burden in their own country.

- Operational Manual 2016 – Global Leprosy Strategy 2016–2020

In March 2017 The Global leprosy programme published its *Monitoring and Evaluation Guide–Global leprosy strategy 2016–2020*. The Global Leprosy Programme is taking the lead in expanding the network for surveillance of leprosy drug resistance, defined as a key intervention under the *Global Leprosy Strategy*.