KUWAIT MEDICAL JOURNAL
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The Official Journal of The Kuwait Medical Association

EDITORIAL

ORIGINAL ARTICLES

CASE REPORTS

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Book

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Book chapter

Philips SJ, Whisnam JP. Hypertension and stroke, In: Laragh JH, Bremner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd Ed. New York: Raven Press; 1995. p 465-478.

Weblinks

U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed June 4, 2003, at http://www.house.gov/reform/min/inves.tobacco/index_accord.htm.)

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Editorial

Openness in Science; Science Set Free

Belle M Hegde
The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*
Manipal University, Manipal India**
The Middlesex Medical School, University of London, UK#
Northern Colorado University, USA##

Kuwait Medical Journal 2016; 48 (4): 290 - 291

"The progress of science, good science, depends on intellectual freedom: science has been very many times advanced by outsiders."

Paul Karl Feyerabend

Science is a craft rather than logic, an enterprise, untidy and fallible. Consequently, science is for sale now as described by David Lewis PhD in his book *Science for Sale.* All these bad traits came to science after science started being secretive, not open fully and is governed by a few people in each science journal called the peer reviewers. These latter decide which is good science and what is bad? How does a peer reviewer understand a new thought as it is not repetitive but refutative? Secrecy in science, plagiarism, fraud in science and the me-too research started after science became an elitist enterprise, after it started the following illogical ideas like patenting for personal benefit, intellectual property rights, and all the bad practices of the monetary economic system. Did Galileo and Archimedes patent their findings? Was not science open then?

One example of science's secretive trend can be gauged by the power of patenting in pharmaceutical drug (so called) research. Today, if the common man is paying billions of dollars for medicines is, purely because of this patenting curse. Similar was the scene in aircraft development before the Second World War. Then the US government brought in pooling patent law. That made it easier and cheaper to search for newer models of fighter planes. Why can't we have such a move now to save the common man from these sharks? Transparency demands openness in research. Today, nearly 90% of all research publications in the leading journals, at least in the medical field, are not reproducible, thereby negating the first principle of science. This has been due to publication of only positive results to satisfy the funding agencies in the industry. The biggest of industries is the cancer industry, where almost 85% positive results are useless as all of them were funded by the industry!

When we talk of medical science, the common man and the medical students believe, and rightly so, that we are honest. Honesty and openness are a rarity in medical science. That apart the very foundation of medical science is faulty as the human system, in systems evolutionary biology, is a closed system which works as a whole. Our research is highly reductionist- a square plug in a round hole! One example will suffice to show how hollow our science is? A new cancer crops up in the human body. To know more about it, what do we do? We cut a small bit of the cancerous growth, crush those cells on a glass slide, stain those with chemicals and kill them completely before looking at them through the microscope to pronounce our learned diagnosis. Based on this faulty technique, we base all our expensive three pronged attack-mutilative surgery, poisonous chemotherapy and destructive radiation.

Let us now scientifically examine, how close to the truth are we in the bargain? Let us imagine a new bird migrates to our neighbourhood. To find out where it came from, where is it headed and why, what is the bird, and what is its fate *etc*. do we kill the bird and study its cells under the microscope? Both in the bird's case and in the case of cancer, what we are looking under the microscope are the dead cells (the

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

tombstone); (Science set free by Rupert Sheldrake). In fact, cancer cells in life work exactly like normal body cells. No one can make out any difference, although when they mutate, their morphology changes, but their function does not! In fact, there is a view that cancer cells are body cells that mutated in the first place, as they could not survive in their environment because of the change in their environment. If that were so, trying to kill them is counter-productive.

As Rabindranath Tagore rightly said, wisdom can grow *ONLY when the mind is free and thoughts are not curtailed or controlled* by peer reviewers. What is the solution? Just as aircraft manufacture pace galloped after pooling patents in that area to get the most needed air force planes, we urgently need to pool pharmaceutical patents because (more important than military aircraft) we need decent, safe and effective drugs for the sick and the infirm. Money makes man mad and greed kills the industry. The next need is to free open access journals from the clutches of the rules and regulations that make it impossible for new journals to survive in this atmosphere of citation index and in fact, the very idea of indexing journals is scientifically obnoxious. Let ideas be free floating and the peer reviewing is done by peers all over the globe. The power of the internet is such that the whole world is the peer reviewer. That will put an end to hatred and filthy criticisms aimed at new ideas which come in the way of the powerful making tons of money by cheating the gullible public. If we did these two and take the attraction of awards, Nobel's, Royal Society Fellowships, I think wisdom would flow relentlessly for the common good of the common man. Otherwise, mankind is doomed by the stranglehold of the so called science very soon. The farsightedness of Benjamin Rush, one of the founder fathers of the American Constitution, was clear in his wanting to have a clause in the constitution to avoid monopoly of any one system to dominate the whole arena. He wanted freedom in the arena of human illness and treatment. The clause was defeated in voting. What Rush had predicted has come true. Western reductionist medical science today has been able to successfully dominate and monopolise the medical field. The ruse that they have taken refuge in is that reductionist science is the only science to rely on. The truth is that while the old natural sciences have all changed completely with the advent of quantum physics, medical science is still mired in ancient reductionism.

"We had the freedom to make mistakes. That's something very important. Unfortunately this freedom for scientists gets more and more lost…. Otherwise you do common things. You don't dare to do something beyond what everybody else thinks."

Heinrich Rohrer

Original Article

Use of Lipiodol to Detect Small HCC not Detected by Other Modalities

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Kuwait Medical Journal 2016; 48 (4) : 292 - 297

ABSTRACT

Objective: This study aimed to apply digital subtraction angiography (DSA) for the detection of early hepatocellular carcinoma (HCC) in an alpha-fetoprotein (AFP)-positive, ultrasonography and/or multi slice computed tomography (MSCT)-negative suspicious population.
Design: Cross-sectional study
Setting: The Second People's Hospital of Jingzhou, Hubei Province, China
Subjects: Sixty-eight cases with continuously and significantly increasing AFP, and no definite or suspected HCC lesions on ultrasonography and/or MSCT examination.
Interventions: All cases underwent DSA; some patients with negative results of DSA were injected approximately 3 - 5 ml lipiodol in the hepatic artery and their CT were reviewed after one month.
Main outcome measures: DSA manifested hepatic artery early to middle period supplying tumor vascular thickening, tortuous or wild disorder, with clearly stained nodules on the edge; the patients were injected lipiodol to find lipiodol deposition.
Results: We detected 58 lesions in 51 cases that were diagnosed as hepatocellular carcinoma *via* DSA and seven lesions in the other 17 cases *via* lipiodol to confirm the diagnosis. Ten cases of hepatocellular carcinoma were excluded.
Conclusion: Detection of early hepatocellular carcinoma with DSA has clinical significance in the high-risk groups with significantly and continuously increasing AFP, ultrasonography and and/or MSCT-negative or suspicious population.

KEYWORDS: AFP, DSA, hepatocellular carcinoma, MSCT, ultrasound,

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant cancers in the world, with the recent annual incidence rate of more than 500,000 cases. It has the third highest death rate among malignant tumors, including lung cancer and gastric cancer, and 20 - 30 million people die of liver cancer every year in our country, with the highest incidence and mortality in the world[1,2]. At present, the treatment of HCC is not satisfactory, partly because of difficulties associated with early diagnosis. Many clinical practices proved that regardless of the treatment modality, early discovery and aggressive treatment of small hepatocellular carcinoma (SHCC) could increase the 5-year survival rate of patients and reduce the recurrence rate. Therefore, early and accurate diagnosis of SHCC is key to the improvement of the survival rates of patients with liver cancer[3,4]. In clinical practice, we observed that ultrasonography or multi slice computed tomography (MSCT) examination did not detect intrahepatic tumor; however, alpha-fetoprotein (AFP) was significantly or continuously increased. Subsequent digital subtraction angiography (DSA) detected local vascular abnormalities or necrotic nodules, indicating that the conversion from single-cell carcinogenesis to tumor that can be detected by imaging must have the characteristic of blood vessels[5]. Therefore, we believe that DSA is more sensitive in the detection of early liver cancer or metastasis compared to ultrasonography and MSCT, which is also the motivation behind this research. In this study, DSA was performed on 68 suspicious high-risk patients

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who were ultrasonography and/or MSCT-negative and significantly or continuously increasing AFP between January 2010 and March 2013. The objective was to investigate the sensitivity and reliability of DSA in the detection of early HCC.

SUBJECTS AND METHODS

Subjects

Between January 2010 and March 2013, DSA was performed on 68 cases negative on ultrasonography (GE LE9, General Electric Company, California, USA) and/or MSCT (Aquilion16, Toshiba Medical Systems Corp., Tochigi, Japan) and suspicious high-risk with significantly or continuously increasing AFP, including 60 men, and eight women in the age range 40 – 80 years with a mean age of 47 years. This study was conducted in accordance with the declaration of Helsinki and also with approval from the Ethics Committee of the People's Hospital. Written informed consent was obtained from all participants.

Screening criteria

The high-risk clinical HCC group refers to the significantly or continuously increasing AFP, and the ambivalent HCC or suspicious early HCC detected on ultrasonography and MSCT. Early HCC refers to SHCC, which is also known as the "sub clinical HCC with a tumor diameter less than 3 cm and no clinical symptoms and signs[6,7].

China's high risk population for HCC included[8-10]: 1) hepatitis B surface antigen positive and over the age of 40 years; 2) chronic hepatitis for more than five years; 3) a history of cirrhosis; 4) with a family history of HCC in relatives over 40 years of age; 5) long-term alcoholics; and 6) area of high liver cancer incidence and high incidence rate in residents of certain age.

The criteria for significantly or continuously increasing AFP were[11,12]: AFP > 400 μg/L, and other causes of significantly or continuously increasing AFP that was clinically excluded, including a slightly increased AFP value >20 μg/L with gradually increasing short-term follow-up, for a sustainable increase.

Materials

Clinical diagnosis was chronic hepatitis and cirrhosis. Liver function Child-Pugh score was A grade for 49 cases, B grade for 14 cases, and C grade for five cases. Sixty-eight patients preoperatively underwent abdominal ultrasonography, as well as plain and enhanced CT scanning, among which 58 cases only showed liver cirrhosis changes on color Doppler ultrasonography, 10 cases showed small focal liver lesions; 29 cases showed no obvious space occupying signs in liver in addition to liver cirrhosis changes on MSCT scan; and 39 cases had 0.9 * 1 cm ~ 3.5 * 4 cm atypical lesions in the liver in addition to liver cirrhosis changes. Alpha fetoprotein (AFP) was 20.5 ~ 1500.5 ng/ml.

Digital Subtraction Angiography

Iategris Allura 12 DSA device was provided by Philips Healthcare (Amsterdam, Holland). Angiography was performed on selective superior mesenteric artery, hepatic artery, and proper hepatic artery; the contrast agent was Omnipaque (GE Pharmaceutical (Shanghai) Co., Ltd., Shanghai, China), with injection rate 4 - 5 ml/s, and a total volume of 10 - 20 ml. When necessary, the catheter was inserted into the right hepatic lobe artery or the left hepatic lobe artery to perform super selective angiography. In patients clearly diagnosed with HCC, a Yashiro Type catheter or Progreat microcatheter (Japanese Terumo Corporation Society, Tokyo, Japan) was super selectively catheterized into hepatic segmental blood supply artery of the tumor lesions. Transcatheter arterial chemoembolization (TACE) treatment was performed by injection of 10 mg pirarubicin and lipiodol emulsion (Pfizer Pharmaceutical (Wuxi) Co., Ltd., Wuxi, China) and 2 - 5 ml ultra-fluid lipiodol emulsion (Guerbet Group, Villepinte, France). Next, depending on the circumstances, the patient was operated on or radiofrequency ablation was performed, and 2 - 3 ml ultra-fluid lipiodol emulsion was injected into the hepatic artery of suspected patients. At the end of one month, abdominal CT was reviewed to observe lipiodol deposition.

RESULTS

Fifty-one out of 68 patients were diagnosed with HCC by DSA, among which 45 cases were with a single lesion; the location was consistent with the lesion in 39 cases suspected by ultrasonography and CT. The other six cases were with multiple lesions, among which five cases had two nodules, and one case had three nodules. In 51 cases, the hepatic arteriography showed normal or thickened vascular branches, and the distal vascular branches were tortuous, coarse, or disordered. Nodule-shaped staining with clear edges was observed with a staining diameter of a few millimeters. The staining duration was more than 15 s (Fig 1). The nodules were larger in patients with vascular disorders compared to those without vascular disorders. Thirty-one cases among these 51 patients were treated with interventional therapy combined with surgery, and other 20 cases were treated with interventional therapy combined with radiofrequency ablation. The remaining 17 patients with negative DSA or only tortuous or coarse distal vascular branches were treated with hepatic

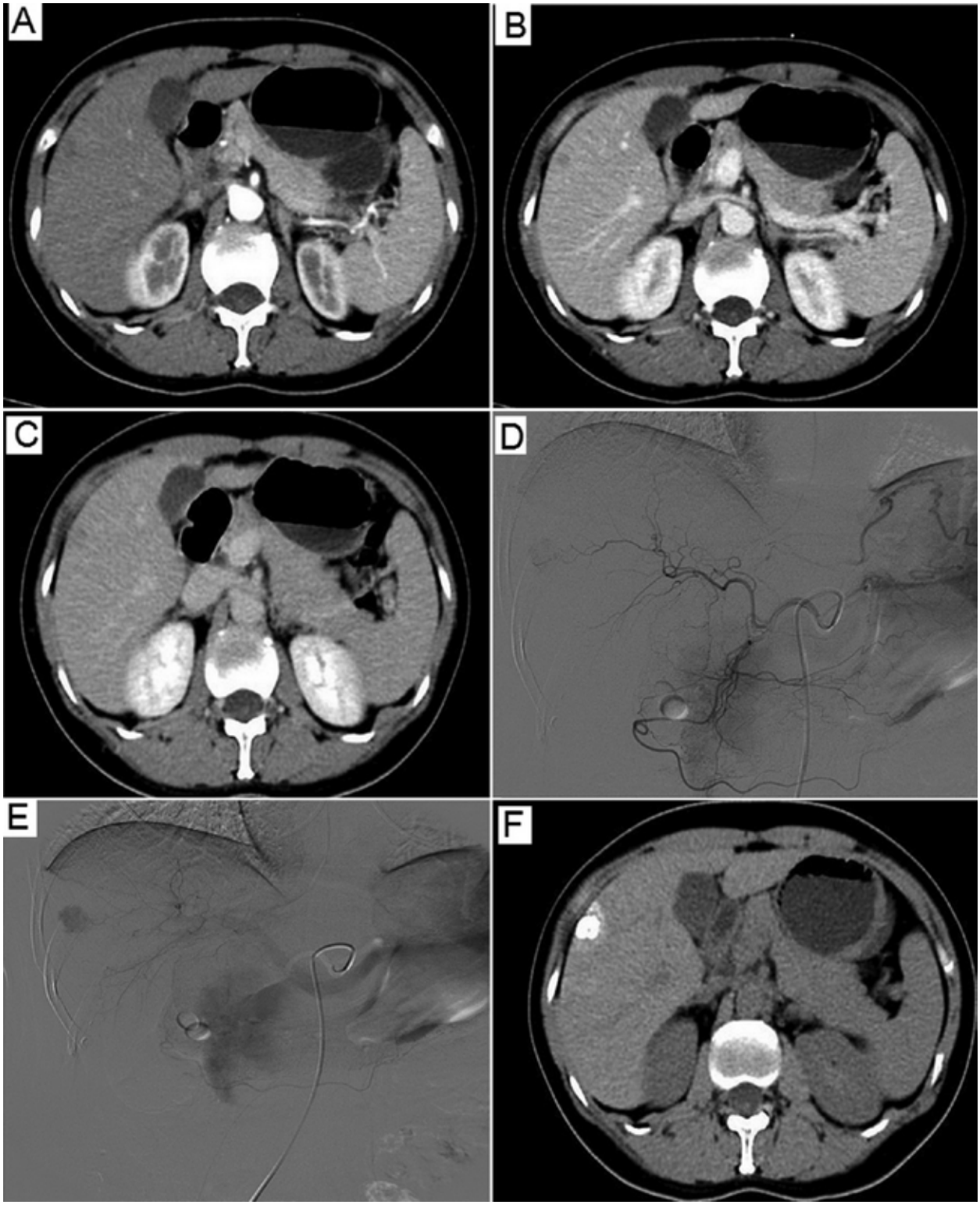

Fig 1: The patient had a history of chronic hepatitis B for 8 years, with AFP of 820 ng/ml. **A, B** and **C:** Liver MSCT showed the occupying lesion in right posterior segment of liver, with properties to be determined; **D** and **E**: Hepatic artery angiography showed nodule-shaped staining in right posterior segment of liver; **F**: CT after TACE.

intra-arterial injection of lipiodol (3 - 5 ml). After one month, the CT reexamination showed seven cases of lipiodol deposition within the lesion, and the surgery confirmed HCC (Fig 2). The other 10 cases were excluded from HCC. The positive rate of HCC directly diagnosed by DSA was 75% (51/68), and that by CT

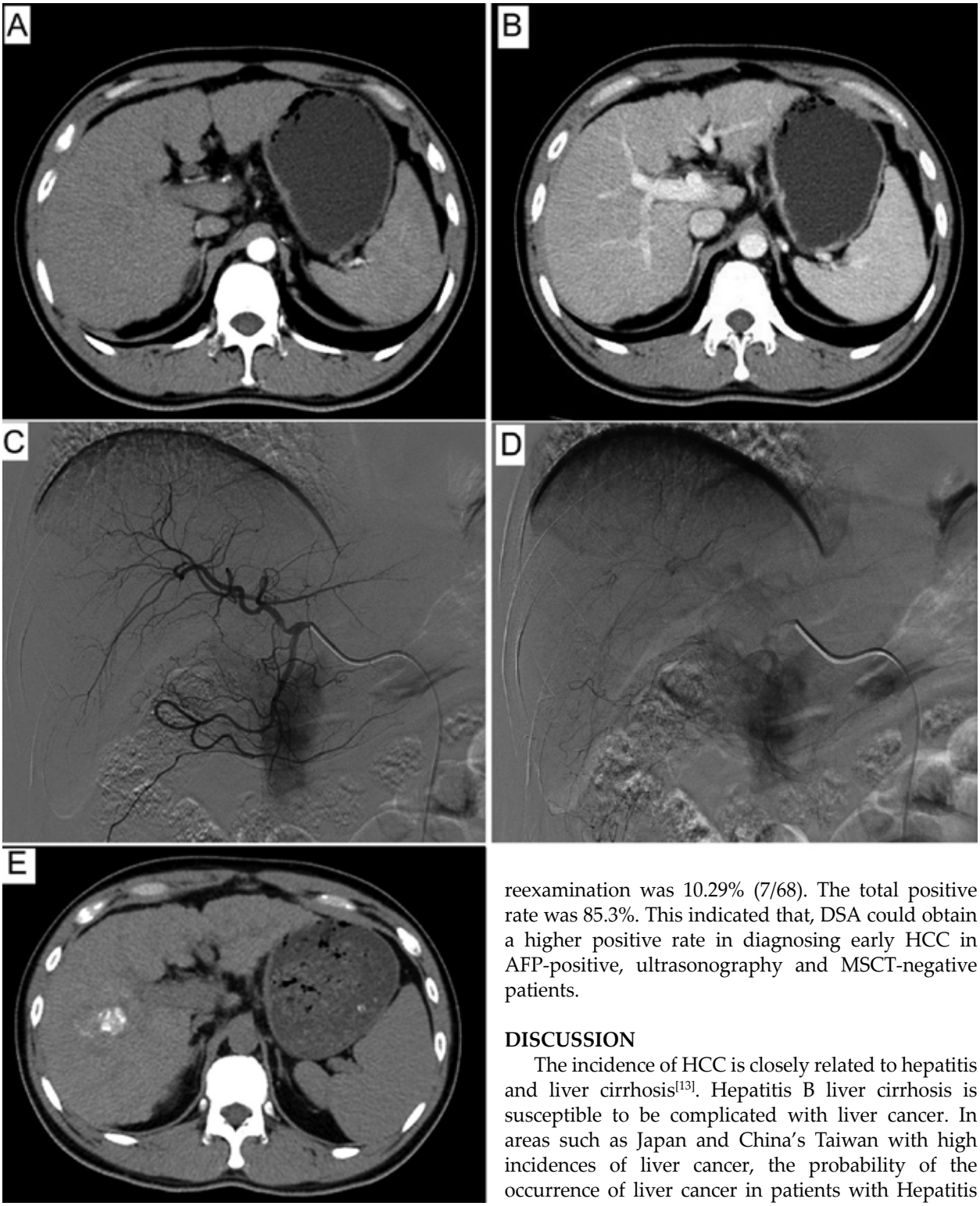

Fig 2: The patient had a history of chronic hepatitis B for 11 years, with AFP of 1650 ng/ml. **A** and **B**: Liver MSCT showed no obvious tumor lesion; **C** and **D**: Hepatic artery angiography showed no tumor staining; **E**: CT showed nodule-shaped iodine oil deposition in right liver 30 days after iodine oil embolization.

reexamination was 10.29% (7/68). The total positive rate was 85.3%. This indicated that, DSA could obtain a higher positive rate in diagnosing early HCC in AFP-positive, ultrasonography and MSCT-negative patients.

DISCUSSION

The incidence of HCC is closely related to hepatitis and liver cirrhosis[13]. Hepatitis B liver cirrhosis is susceptible to be complicated with liver cancer. In areas such as Japan and China's Taiwan with high incidences of liver cancer, the probability of the occurrence of liver cancer in patients with Hepatitis B surface antigen-positive cirrhosis can reach 2.18% ~ 6.16%[14]. Prognosis and survival in cirrhotic patients with HCC complications are directly related to early diagnosis and timely treatment. Currently, in order to clinically assess whether liver cirrhosis is associated with HCC complication, B ultrasonography, CT, MRI, and AFP determination are used. However, existing

data shows that B ultrasonography and CT have rates of misdiagnosis as high as 90.2% and 89.5%, respectively, for tumors of diameter ≤1 cm[15-17]. When the liver lesions are found using B ultrasonography or CT image examination, the AFP value plays a supporting role in the diagnosis of liver cancer; while AFP was weakly positive (20 ~ 200 ng/L), the report of HCC is not in the minority[18]. The liver carcinogenesis of cirrhosis is a multistage process which involves the formation of regenerative nodules in liver cirrhosis basis, developing into dysplastic nodules, and ultimately into early HCC. Because of the change in blood perfusion at different stages, CT or MRI expression is significantly different. The manifestation is not typical and difficult to diagnose. Although it is reported in the literature that DSA has higher sensitivity for the diagnosis of primary liver cancer than the CT [19], when the patients are not diagnosed with HCC in B ultrasonography, CT and AFP, they may not accept invasive DSA examination. Therefore, at this stage, DSA is not yet established as the main means of diagnosis. In the group of patients with hepatic cirrhosis where a clear diagnosis of small hepatic lesions using B ultrasonography and CT could not be made but AFP significantly increased and continued to increase, patients were informed of consent and underwent DSA. The purpose was to investigate the sensitivity and reliability of DSA in the detection of early HCC in AFP-positive, ultrasonography and MSCT-negative patients or suspicious populations. In this study, 51 out of 68 patients were diagnosed with HCC using DSA, among whom 45 cases were with a single lesion, and the location was consistent with the lesion in 39 cases suspected by ultrasonography and CT. The other six cases were with multiple lesions, among which five cases had two nodules, and one case had three nodules. In these 51 cases, the DSA showed normal or thickened vascular branches, and the distal vascular branches were tortuous, coarse or disordered. There was nodule-shaped staining with clear edges, and the staining diameter was a few millimeters. The staining duration was more than 15 s. The remaining 17 patients with negative DSA or only tortuous or coarse distal vascular branches were treated by hepatic intra-arterial injection of lipiodol (3 - 5 ml). After one month, the CT reexamination showed seven cases of lipiodol deposition with AFP decrease inside the lesion, and the surgery confirmed HCC. The other 10 cases were excluded from HCC. The CT showed high-density shadow of intrahepatic lesser nodules. In these 10 cases, the lipiodol deposition is mainly due to the phagocytic cells in normal liver sinus, and can be removed within a few days. However, the blood vessels in tumor tissue, lack of nerve innervations and smooth muscle, and the blood vessel wall is rough, and cannot easily remove the iodine oil. In addition, the tumor lacks normal lymph and reticuloendothelial tissue, and cannot timely phagocytize, transform and eliminate the intratumoral iodine oil.

The tumor tissue of HCC has the characteristic of producing angiogenesis factors to form a large number of blood-supply vessels, which transform from single cell carcinogenesis into a visible 2 mm tumor[20,21]. Therefore, the early detection of blood-supply vessels is helpful for diagnosis of early tumor. Hepatic artery angiography is an invasive inspection method. It can not only display the characteristic of intrahepatic lesion, but also the extent, size and number of lesion. Especially, it has higher sensitivity and specificity in diagnosis of tumors with diameters less than 1 cm compared with other imaging methods, and the interventional therapy can be performed immediately[22]. In this study, the total detection rate using DSA was 85.3%, which is significantly higher compared to ultrasonography and CT examination. Therefore, DSA has a clinical significance when HCC cannot be confirmed by other routine examination methods. Based on the sensitivity of angiography and its characteristics, DSA examination has a peculiar effect in the early diagnosis of HCC and early TACE treatment. In the group of patients with DSA examination the higher detection rate observed may be related to the following factors: 1) the long time-histories observation, and the full staining of the small blood vessels; 2) continuous observation that is more conducive to the dynamic performance of vascular characteristics; and 3) the individualization of observation time. Because the tumor blood of patients varies with different conditions, and have different vascular staining speeds, the fixed scan time in CT enhancement may not be appropriate for monitoring patient specific blood supply; therefore, some small vessels that are stained are omitted from the observation period, which can result in misdiagnosis from the images. Therefore, DSA should include TACE function in the treatment. At the same time, DSA examination can detect early abnormalities of blood vessels, and be more sensitive to early detection of liver cancer and liver metastases nodules especially in high-risk populations of HCC with significantly and continuously increasing AFP, negative CT and MSCT and suspicious populations from the clinical HCC, in order to obtain the best treatment effect.

This study suggests that, DSA is more sensitive to the detection of SHCC, which is difficult to diagnose with B ultrasonography and CT. Timely application of DSA can improve the detection rate of early HCC. The early onset of liver cancer is insidious, and clinical symptoms are not typical. If ultrasonography and CT reveal no lesions, which are often not paid sufficient attention

to, or small atypical lesions are observed passive dynamically or patients are reluctant to undergo further tests, these methods are inadvisable. We think that DSA can be recommended to determine whether there is HCC under the following circumstances: 1) the liver cirrhosis patients who were clinically suspected of HCC, with continuously strong positive AFP, but the B ultrasonography and CT examination found no liver lesions, 2) The ultrasonography and CT found lesions in the liver that was highly suspected to have HCC and lacked typical manifestations.

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Original Article

Evaluation of Urodynamic Parameters in Patients with Anterior Vaginal Wall Prolapse

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ABSTRACT

Objectives: To investigate the urodynamic features in women with anterior vaginal wall prolapse and to compare with prolapse degrees and obtained urodynamic signs in this grup.
Design: Prospective study
Setting: Ministry of Health Bakırkoy Dr. Sadi Konuk Training and Research Hospital
Subjects: A total of 395 neurologically intact women with anterior vaginal wall prolapse were evaluated. Cystosel stage was graded according to pelvic organ prolapse quantification (POP-Q). They were divided into three groups: Stage I (n = 165), II (n = 150) and III (n = 80).
Intervention: Full multichannel urodynamic test
Main outcome measure: Urodynamic parameters
Results: Incontinance was established 76% in stage I, 72% in stage II, and 67% in stage III patients. Residuel urine volume was too much in stage III compared to stage I and II, respectively (p = 0.001, p = 0.029). The urodynamic paramethers (the first sensation to fill, the first desire and the strong desire to void) were less in stage I than stage II and III, respectively (p = 0.011, p = 0.039 and p = 0.008). The maximum bladder capacity (up to 300 ml.) was much more in stage III than stage 1 and 2 (p = 0.047).
Conclusions: Our study showed that the anterior vaginal wall prolapse can be together with incontinance even if it is at the begining stage. Also, the sensation of the bladder reduces with the increase in the stages of the anterior vaginal wall prolapse and it can mask the incontinance signs. The women with large anterior wall prolapse may have a weak detrusor contraction and a high postresidual urine volume.

KEY WORDS: detrusor overactivity; overactive bladder; pelvic organ prolapse; urodynamic study; stress urinary incontinence

INTRODUCTION

Pelvic floor dysfunction refers to a wide range of clinical conditions including urinary incontinence (UI), pelvic organ prolapse (POP), other functional disorders related with lower urinary tract and defecation and comprises 43 - 76% of patients referring to gynaecology outpatient unit[1]. Anterior vaginal wall prolapse including cystocele, urethrocele and anterior enterocele concepts is described as prolapse (sinking) of vaginal anterior wall and overlying bladder floor toward vagina. Probable etiology of pelvic relaxation hasn't been clearly understood yet; however, it is supposed to be multifactorial and vaginal delivery is pointed out as the most common reason. UI is described as involuntary urine flow which becomes a distressing social and/or hygienic problem[2]. Prevalence of UI is estimated at around 30%[3]. Although it's not a life threatening health condition, it may cause distress due to persistent wetness and irritation and emotional problems up to depression resulting from these situations[4].

POP and stress urinary incontinence (SUI) may be present in females up to 15 - 80%[5]. In POP cases, obstructive urinary dysfunction and over active bladder (OAB) complaints are observed more frequently than normal population[6].

Incontinance may occur in women with severe POP after surgery. Thus, International Continence Society

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(ICS) and International Incontinence Consultation (IIC) clearly recommend urodynamic assessment before doing operations due to pelvic organ prolapse[7,8]. Particularly in anterior compartment prolapse, stretching of urothelial receptors due to descent of trigon toward vaginal anterior wall and/or urethral obstruction may lead to detrusor contraction[6,9]. Also, OAB symptoms usually increase after POP repair[10].

In addition to revealing occult urodynamic stress incontinence, preoperative urodynamic test may pave the way for adding specific surgical procedures to treatment, when required; though it's controversial. It may also facilitate diagnosis of patients with concomitant detrusor over activity, who may need anti-muscarinic drug treatment. Cost-effectiveness of preoperative urodynamic test is still an important issue in debates[11]. Some authors are recently in search of alternative diagnostic methods less invasive related to urodynamic test (measurement of bladder wall thickness and specific questionnaire forms containing prolapse and incontinence etc.)[12,13].

It may be predicted that increasingly more women will seek help for one or more pelvic floor disorders or refer to a doctor for these disorders, because women more actively involve in social life, older female population increases and there will be growing demand for more active life and higher life quality. Keeping these information in mind, our aim is to determine the effect of anterior vaginal wall prolapse stage over urodynamic test results.

SUBJECTS AND METHOD

This study was done in Ministry of Health Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Obstetrics and Gynaecology Department during February 2008 – August 2011 in 29 - 89-year-old patients referring for POP and/or UI complaints. Ethics committee approval of the hospital in which the study was designed was taken.

Inclusion criteria for the study

1. Absence of co-existing metabolic disease (severe or uncontrolled diabetes, peripheral neural involvement due to diabetes)
2. Absence of neurologic disorders (active demyelinating diseases, multiple sclerosis, previous spinal cord trauma, intracerebral bleeding, clinically overt peripheral neuropathies)
3. Absence of pregnancy or suspected pregnancy
4. Not taking medical treatment for diagnosis of incontinence
5. Not to have undergone an anti-incontinence surgery
6. Absence of mechanical obstruction in bladder (urethral stricture, cancer, stone)
7. Absence of previous pelvic radiotherapy, and
8. Absence of untreated urinary tract infection.

Assessment and follow up of patients were performed in five stages as medical history taking, laboratory tests (complete urinary analysis, urine culture and sensitivity tests), uro- gynaecologic and neurologic examination, voiding diary and urodynamic tests.

In general, history taking age, menstrual status, number of deliveries, type of delivery (vaginal, vacuum/forceps, cesarian section), previous operations, and presence of chronic diseases were sought. In urogynecologic history taking, duration of incontinence and prolapse, self-reported probable reasons precipitating incontinence, if present, previous medical and conservative treatment for incontinence and/or prolapse, duration of treatment, acquired benefits, if present, conditions increasing or decreasing incontinence and prolapsed complaints, previous urogynecologic operations, family history, effects of symptoms on life quality, number of pads and protective tools that are used, fluid intake, particularly caffeine intake, intake of other drinks having diuretic properties, constipation, urge urinary incontinence (UUI) and SUI were sought. Weight and height of all patients were measured and body-mass index was calculated. Complete urinary analysis, urine culture and sensitivity tests, fasting blood sugar, renal (urea, creatinine), hepatic [Serum Glutamat Oxalacetat Transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT)] function tests were done, before including the patients into the study. Patients with abnormal biochemistry parameters were excluded from the study after consultation with the pertinent departments. Treatment was planned for patients having urinary tract infection.

In gynaecologic examination, urethrocele, cytocele in vulva and anterior vaginal wall and enterocele and rectocele in posterior wall and also descending uterus were sought in straining patients . Pelvic Organ Prolapsus Quantification (POP-Q) staging was used in prolapse assessment. The patients were assessed in standard gynaecologic table while they are at dorsal lithotomic position; subsequently, the examination was repeated in standing position. In POP-Q test, reference points related to hymen was assessed during maximum straining using speculum and ruler. Six reference points in vagina were assessed in centimetre (cm) unit related to their distance to hymen. Measurements at proximal relative to hymen were considered negative and measurements at distal positive. Hymen was considered as zero, since it is the reference point. Positive and negative values were between -3 and +3. Vaginal supportive tissues and defects were assessed separately in all regions (vaginal

apex, anterior wall, posterior wall and perineum). Specific measurements of six points on vagina and three points on perineum (total nine points) were placed in a 3 x 3 table[11]. Stress test was applied to the patient by observing urine leakage while the patient is coughing. Anatomic position of urethra and presence of hypermobility were sought by performing Q-Tip test using a sterile, well-lubricated cotton-tipped swab. In neurologic examination, sensitivity of mons pubis, perineum, perirectal region and inner surface of thigh, anal sphincter tonus, bulbocavernous and anocutaneous reflexes and motor and sensory pathologies of the lower extremities were checked in order to assess sacral S2-4 functions. Muscle strength of perineum was measured by ordering patient to squeeze two fingers of examiner inside vagina. In this test perineum muscle strength was scored as 0/5 - 5/5. Pad test was performed.

It was instructed that voiding diaries should be completed by patients at least for three days. Information about number of micturition during daytime and night, continence, amount of fluid intake, amount of voided urine, number of pads in case they are used were included in voiding diaries.

Urodynamic test was done in compliance with standard recommendations of ICS. The rationale, details and stages of the test were explained to the patient and written informed consent form was taken from the patient. The test was performed by using multichannel urodynamic instrument available in our clinic (MMS Solara, Ankara, Turkey). In all patients uroflow and post-voiding residual urine were measured after spontaneous normal desire to urinate. In uroflow evaluation time to maximum flow, maximum flow rate, amount of voided volume and average flow rate were measured.

After uroflow evaluation the patient was transferred to lithotomy table and sterile 6F 3 way cystometry catheter was inserted into urethra after perineum cleansing while the patient is in semi sitting position. Urodynamic test was done after correction of prolapse of the patients without compressing urethra by using a simple padding of appropriate dimensions. The bladder is filled by saline at room temperature by 50 ml/min rate and the patient was asked to cough in every 100 ml. Urine leakage during coughing or urine leakage due to uninhibited detrusor contractions while non-coughing was recorded whenever it's observed.

By cystometry first desire to void (ml), urgency (ml), severe desire to void (ml), presence of pain, maximum detrusor pressure, uninhibited contractions, abdominal leakage pressure (ALPP), bladder capacity (ml) and bladder compliance (ml/cmH_20) were determined. Detrusor pressure was automatically calculated by computer by using Pdet = Pves - Pabd formula. After reaching to maximum cystometric capacity, filling csytometry was terminated. Subsequently, pressure flow study was performed while the patients were in sitting position or standing. Detrusor contractility, voiding pressure at maximum flow and maximum voiding flow rate were recorded and residual urine was again measured. If maximum flow rate (Qmax) is >15 ml/sec, flow curve is normal and if voiding volume is >150 ml, uroflow is regarded normal. Idiopathic detrusor overactivity is described as involuntary increase in detrusor pressure related with sudden desire to void and urine leakage or an increase of 15 cmH_2O or more in pressure without this desire. Bladder compliance was calculated in accordance with standards recommended by ICS.

Urodynamic Stress Incontinence (USI) is described as presence of urinary incontinence without involuntary detrusor contraction during coughing or increasing intraabdominal pressure by valsalva while bladder has 250 - 300 cc urine volume.

Statistical evaluation

Statistical analysis of this study was done by using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In evaluating values descriptive statistical methods (mean, standard deviation) were used and also Tukey multi comparison test was used for inter-group comparisons in one way variance analysis subgroup comparisons and chi-square and Fisher exact test for comparison of qualitative data. $P < 0.05$ was considered as statistically significant.

RESULTS

Three hundred and ninety-five patients having POP were included into the study; according to POP-Q staging, 165 were stage 1, 150 stage 2 and 80 stage 3.

Table 1: Demographic characteristics of cases according to POP-Q stage (n:395)

Characteristics	Stage-1	Stage -2	Stage -3	F	p-value
Age	50.66 ± 10.18	51.44 ± 10.36	56.49 ± 11.1	8.67	0.0001*
Height (cm)	159.55 ± 5.56	157.64 ± 7.08	158.23 ± 6.03	3.71	0.025*
Weight (kg)	77.25 ± 11.02	75.21 ± 11.44	73.15 ± 11.69	3.59	0.029*
BMI (kg/cm^2)	30.43 ± 4.7	30.29 ± 5.02	29.12 ± 4.2	2.08	0.126

(BMI: Body mass index, data are as mean ±standard deviation, one way variance analysis, *: $p<0.05$)

Mean age of stage 3 group was significantly higher than other groups (p = 0.002, p = 0.0001); however, there was no significant difference between stage 1 and stage 2 groups (p = 0.787). Mean height of stage 1 group was higher than stage 2, and the difference was statistically significant (p = 0.021). There was no significant difference between other groups (p > 0.05). Mean body weight of stage 1 was found to be significantly higher than stage 3 group (p = 0.026), however, there was no significant difference between other groups (p > 0.05). There was no significant difference between groups regarding body mass index (BMI) (p = 0.126). In stage 1 and stage 2 groups average parity is 2 (minimum: 1, maximum: 6), in stage 3 average parity is 3 (minimum: 1, maximum: 9). Correlation between POP-Q stage and demographic characteristics of patients were summarized in Table 1 and Tukey multiple comparison analysis revealed that the POP-Q stages were influenced by age, height and weight in Table 2. Diagnostic distribution of patients is summarized in Table 3 and between them no difference was observed (p = 0.412).

Table 2: Tukey multiple comparison analysis revealed that the POP-Q stages were influenced by age, height and weight.

POP-Q stage	Age	Height	Weight
Stage 1 / Stage 2	0.787	0.021*	0.252
Stage 1 / Stage 3	0.000*	0.293	0.026*
Stage 2 / Stage 3	0.002*	0.786	0.404*

(*: p<0.05)

There was statistically significant difference between groups in respect of post void residual urine(PVR), first desire to void, normal desire to void and strong desire to void (Table 4). In stage 3 group, PVR average was found to be significantly higher compared to other groups (p = 0.001, p = 0.029); on the other hand, in stage 1 group, average first desire to void was found to be significantly lower compared to other groups (p = 0.019, p = 0.042). There was no significant difference between groups regarding average maximum bladder capacity (p = 0.099). Normal desire to void and strong desire to void averages were found to be significantly lower in stage 1 group (p = 0.049, p = 0.043; p = 0.027, p = 0.023). The comparison of bladder volumes according to POP-Q stages is showed in table 5.

There was statistically significant difference between groups regarding PVR distribution and maximum bladder capacity distribution. In stage 3 group, > 50ml PVR and > 300ml 'maximum bladder capacity' was significantly higher compared to other groups. There was no statistically significant difference between groups in respect of 'first desire' distribution (p = 0.238) (Table 6). Valsalva leak point pressure (VLPP), maximum rate (ml/sec), time to maximum rate (sec) and flow duration (sec) averages and detrusor pressure during maximum flow (cmH_2O) were not significantly different between groups. However, in stage 1 group, average urine

Table 3: Distribution of urodynamic diagnosis according to POP-Q Stages (n=395, χ^2 test).

Diagnosis	Stage 1		Stage 2		Stage 3		
	n	(%)	n	(%)	n	(%)	
Normal	40	(24.40)	42	(28.20)	26	(33.80)	
Over active bladder	36	(22.00)	31	(20.80)	20	(26.00)	
Stress incontinence	53	(32.30)	38	(25.50)	18	(23.40)	χ^2 : 6.1
Mixed incontinence	35	(21.30)	38	(25.50)	13	(16.90)	p = 0.412

Table 4: Bladder volume values according to POP-Q Stages

Bladder volume (ml)	Stage-1	Stage -2	Stage -3	F	p-value
PVR	37.59 ± 63.37	47.43 ± 68.29	73.1 ± 80.71	6.45	0.002*
Max. Capacity	420.37 ± 125.64	435.93 ± 132.41	458.51 ± 128.01	2.33	0.099
First sensation	150.67 ± 90.13	179.34 ± 93.71	180.07 ± 95.3	4.53	0.011*
Desire	233.94 ± 111.38	260.9 ± 110.74	267.4 ± 106.91	3.26	0.039*
Severe desire	332.44 ± 114.92	367.07 ± 113.36	375.38 ± 115.92	4.95	0.008*

(PVR: post voiding residual urine, Max Capacity: Maximum bladder capacity; data are as mean ±standard deviation, one way variance analysis, *p<0.05)

Table 5: Comparison of bladder volumes according to POP-Q Stages

POP-Q stages	PVR	First sensation	Desire	Severe desire
Stage 1 / Stage 2	0.439	0.019*	0.049*	0.027*
Stage 1 / Stage 3	0.001*	0.042*	0.043*	0.023*
Stage 2 / Stage 3	0.029*	0.998	0.912	0.870

(Tukey Multiple Comparison Test, *p<0.05)

Table 6: Urodyinamic parameter (PVR, maximum bladder capacity and first sensation) values within normal range and exceeding these limits in stage 1-2-3 patients

Urodyinamic parameter	Values (ml)	Stage 1		Stage 2		Stage 3		
		n	(%)	n	(%)	n	(%)	
PVR	< 50	122	(79.70)	109	(76.80)	39	(54.90)	χ^2 : 16.5
	> 50	31	(20.30)	33	(23.20)	32	(45.10)	P = 0.0001*
Maximum bladder capacity	< 300	30	(18.30)	20	(13.40)	5	(6.50)	χ^2 : 6.11
	> 300	134	(81.70)	129	(86.60)	72	(93.50)	P = 0.047*
First sensation	< 150	79	(49.10)	62	(42.80)	28	(37.80)	χ^2 : 2.87
	> 150	82	(50.90)	83	(57.20)	46	(62.20)	P = 0.238

(PVR: postvoiding residual urine volume, χ square, *: p<0.05)

Table 7: Urıdynamic parameters in Stage 1-2-3 patients

Urodynamic parameters	Stage 1	Stage 2	Stage 3	F	p-value
VLPP (cmH_2O)	75.6 ± 92.34	63.4 ± 56.02	71.79 ± 56.73	0.57	0.566
Maximum flow rate (ml/sec)	27.77 ± 11.83	25.79 ± 11.89	25.78 ± 11.76	1.11	0.331
Time to Maximum rate (sec)	12.32 ± 13.38	14.17 ± 15.7	13.36 ± 22.19	0.41	0.664
Flow duration (sec)	39.26 ± 23	46.05 ± 24	44.97 ± 31.89	2.55	0.08
Pdet at maximum Flow(cmH_2O)	18.48 ± 26.26	22.99 ± 53.74	22.61 ± 25.29	0.47	0.624
Mean Flow Rate (ml/sec)	14.84 ± 7.24	12.41 ± 6.87	12.99 ± 7.45	3.92	0.021*

(data are as mean ± standard deviation, one way variance analysis, *: p <0.05), VLPP : valsalva leak point pressure

flow rate (ml/sec) was significantly higher than other groups (p = 0.021) (Table 7). VLPP distribution and detrusor pressure during maximum flow were not statistically different between groups (p = 0.745, p = 0.115) (Table 8).

Detrusor opening pressure, detrusor leak point pressure, Bladder Outlet Obstruction Index (BOOI), Bladder Contractility Index (BCI), functional urethral length and maximum urethral closure pressure (MUCP) averages were not statistically different between groups (Table 9). Detrusor opening pressure, detrusor leak point pressure, BOOI and BCI distribution between groups were not statistically different (Table 10).

DISCUSSION

In this study, 395 patients having various stages of anterior vaginal wall prolapse, urodynamic evaluation was done in order to study lower urinary tract system functions and urodynamic findings were assessed.

Table 8: Range of VLPP and detrusor pressure at maximum flow parameters according to POP-Q Stages

Maximum flow parameters		Stage 1		Stage 2		Stage 3		
		n	(%)	n	(%)	n	(%)	
VLPP (cmH_2O)	<60	59	(62.80)	48	(61.50)	19	(57.60)	
	60-90	8	(8.50)	11	(14.10)	5	(15.20)	χ^2 : 1.95
	>90	27	(28.70)	19	(24.40)	9	(27.30)	p = 0.745
pdetQmax (cmH_2O)	<100	128	(100.00)	116	(96.70)	60	(98.40)	χ^2 : 4.32
	>100	0	(0)	4	(3.30)	1	(1.60)	p = 0.115

(pdetQmax: detrusor pressure at Maximum flow, χ square, p>0.05), VLPP : valsalva leak point pressure

Table 9: Values of Pressure flow study and urethral pressure profile parameters in stage 1-2-3 patients

Parameters	Stage 1	Stage 2	Stage 3	F	p-value
Detrusor opening pressure	18.65 ± 23.6	16.55 ± 33.66	18.28 ± 21.77	0.19	0.828
Detrusor leak point pressure (cmH_2O)	10.31 ± 14.92	13.39 ± 19.73	11.36 ± 24.86	0.40	0.674
BOOI (PdetQmax-2Qmax)	-37.41 ± 40.23	-29.39 ± 57.4	-30.44 ± 35.66	1.05	0.350
BCI (PdetQmax+5Qmax)	155.75 ± 58.45	151.98 ± 81.2	149.23 ± 62.42	0.22	0.803
Functional urethral length (mm)	29.46 ± 4.8	33.41 ± 12.16	35.09 ± 20.18	1.74	0.183
MUCP (cmH_2O)	81.23 ± 28.31	76.49 ± 28.5	78.08 ± 20.57	0.28	0.756

BOOI (bladder outlet obstruction index) is calculated by (PdetQmax-2Qmax) formula. BCI (bladder contractility index) is calculated by (PdetQmax+5Qmax) formula. MUCP (maximal urethral closure pressure) data are as mean ±standard deviation, one way variance analysis *: p<0.05)

Table 10: Distribution of Detrusor opening pressure, Detrusor leak point pressure, BOOI and BCI range among Stage 1-2-3 patients

Distribution		Stage 1		Stage 2		Stage 3		
		n	(%)	n	(%)	n	(%)	
Detrusor opening pressure (cmH_2O)	< 80	126	(100.00)	116	(99.10)	60	(100.00)	χ^2 : 1.6
	> 80	0	(0)	1	(0.90)	0	(0)	p = 0.450
Detrusor leak point pressure (cmH_2O)	< 40	59	(96.70)	53	(93.00)	23	(92.00)	χ^2 : 1.11
	> 40	2	(3.30)	4	(7.00)	2	(8.00)	p = 0.574
BOOI (PdetQmax-2Qmax)	< 20	127	(95.50)	116	(94.30)	64	(97.00)	
	20 - 40	4	(3.00)	4	(3.30)	1	(1.50)	χ^2 : 0.89
	> 40	2	(1.50)	3	(2.40)	1	(1.50)	p = 0.926
BCI (PdetQmax+5Qmax)	< 100	20	(15.00)	21	(17.10)	12	(18.20)	
	100 - 150	43	(32.30)	47	(38.20)	26	(39.40)	χ^2 : 2.48
	> 150	70	(52.60)	55	(44.70)	28	(42.40)	p = 0.648

BOOI (bladder outlet obstruction index) is calculated by (PdetQmax-2Qmax) formula. BCI (bladder contractility index) is calculated by (PdetQmax+5Qmax) formula.

In a series of 237 patients analysis of POP severity and POP region and other co-existing function disorders were carried out and it was determined that 73% of patients with POP have a type of (13% stress, 3% urge, 76% mixed) urinary incontinence[14]. In another study evaluating SUI prevalence and abdominal leak point pressure (ALPP) values in patients with advanced stage POP, SUI prevalence was found as 50%[15].

In all epidemiologic studies, BMI was found to be correlated with urinary incontinence. Mant *et al* have performed a cohort study in 17,032 women between 25 - 39 years old referring to family planning clinic to investigate POP epidemiology and have shown that weight increase plays a significant role in development of prolapse and risk of POP development is 2.51 times more in women with a body mass index (BMI) 25 - 30 and 2.56 times more in women with a BMI > 30[16]. In our study, there was no statistical difference between groups in respect of BMI averages.

Ebbesen *et al* have determined that POP incidence and prevalence increase by increasing age[17]. In a cross sectional study performed in 27,232 women participating WHI hormone replacement therapy study, it has been shown that prolapse was 1.2 times more in 60 - 69 years old group compared to 50 - 59 years old group and 1.4 times more in 70 - 79 years old group[18]. In our study, in line with the literature, it was observed that when POP-Q stage increases, mean age of patients also increase.

It can be due to some complications during urodynamic procedures. Klingler *et al* have performed a prospective study in 63 male and 56 female patients who had undergone pressure flow study (PFS) to investigate morbidity and complications of urodynamic evaluation and have found that urinary retention, macroscopic hematuria, UTI and fever rate were 19% in males and 1.8% in females[19]. In our cases, there were no complications associated with urodynamic evaluation in 395 patients who had undergone urodynamic test and PFS.

PVR urine is rare in females. In 5% of normal female population and 13% of women experiencing incontinence, there was residual urine > 30 ml[20]. In a study comparing cases of SUI, 47 cases of advanced stage POP without SUI and 78 cases without any urologic symptom regarding urodynamic results mean PVR value was 12 ml in stage 3 - 4 POP-Q cases and 0 ml in control cases[21]. PVR urine > 50 ml is a finding in favour of weak detrusor activity. In this study, in 45.1% of patients of stage-3 POP group, residual urine was over 50 ml and the rates were respectively 23.2% and 20.3% in stage 2 and stage 1 patient group.

In normal conditions, first desire to void occurs when there is 150 - 200 ml urine in the bladder. In another study, cystometry was performed in 60 patients with stage 3 - 4 POP before and after reduction of prolapse and maximum bladder capacity was found as 351 ml before correction of prolapse and 352 ml after correction of prolapse by pessary[4]. In our cases, first desire to void, normal desire to void and maximum bladder capacity averages were found to be in normal range in patients with stage 1, 2 and 3 POP. It may be suggested that when prolapse stage increases, bladder sensitivity decreases due to weakening detrusor activity. Occasionally, along with aging, sensation decrease may occur due to replacement of bladder smooth muscle by collagen[22]. Urethral obstruction due to prolapse lead to weakening in detrusor muscle in time; consequently chronic urethral resistance due to prolapse may cause decreased activity in detrusor muscle or hypocontractility[23]. Also in this study, it was observed that bladder volume and residual urine values didn't reach to pathologic levels, but they increased as the stage of prolapse increase, though remaining in the normal range. Thus, while

planning surgery, it is necessary to be vigilant about the probability of a contractile bladder or sensation decrease at times.

For anatomic stress incontinence, VLPP > 90 cmH_2O and for sphincter insufficiency, VLPP < 60 cmH_2O are considered as a reliable criteria[24]. In our study, it was observed that in patients with prolapse, SUI may develop due to intrinsic sphincter insufficiency in addition to anatomic stress incontinence.

Uroflowmetry and PFS are not as practical in females as in males; because in females, only 4% of lower urinary tract disorders are associated with voiding dysfunction. In a study investigating voiding mechanisms and effects of anterior vaginal wall prolapse on detrusor contraction during voiding in continent females and women with SUI, it was determined that women with SUI void with weaker detrusor contraction compared to continent women[25]. Various criteria describing obstruction were reported relying upon pressure flow studies. Groutz *et al* described obstruction as maximum free urine flow < 12 ml/sec and detrusor pressure > 20 cm H_2O under maximum flow[26]. When PdetQmax = 35 cmH_2O and Qmax < 15 ml/sec, specificity for bladder outlet obstruction is 93.9% and sensitivity 81.6%[27].

Advanced stage anterior vaginal wall prolapse may change voiding phase parameters and may lead to voiding dysfunction; however in the literature, publications studying voiding phase measurements and parameters in women with prolapse are scarce[28,29]. Romanzi LJ *et al* have performed a study to investigate effects of genital prolapse on voiding parameters and applied PFS and Qtip test to 35 (58%) women with stage 1 - 2 prolapse and 25 (45%) women with stage 3 - 4 prolapse and have reported that urethral hypermobility and voiding difficulty symptoms and detrusor overactivity were more frequent in stage 3 - 4 women compared to stage 1 - 2 women[29]. In a study comparing PFS results of 47 cases with stage 3 - 4 prolapse, but without incontinence with PFS results of urologically healthy control group; in advanced stage group, maximum flow rate (ml/sec) was 20.5 ± 9.6 and in controls 27.7 ± 9.3 and it is observed that there was statistically significant difference between groups[30]. In our study, even though a significant difference in respect of maximum flow rate has not been observed; similar to Narihito's study, maximum flow rate decreased as stage of prolapse increased. This may be interpreted as a gradual decrease in voiding rate due to increased urethral resistance caused by POP.

In 70 SUI cases, evaluation by urodynamic tests before and after surgical correction of SUI has revealed that only a few of the patients voided with low pressure but regained normal voiding rate after the operation[28]. Chaikin *et al* have performed a study to investigate anti-incontinence surgery indications and reported that there was no decrease in detrusor pressure in patients with POP and after correction with pessary bladder outlet obstruction wasn't observed in any of the patients[31]. In this study, there was no statistically significant difference between groups. It can be concluded from our study, that patients with prolapse, void with low average rate, thus their detrusor activity is weak. Since there are no definite criteria for obstruction in females, if > 100 cmH_2O is regarded as a cut off point; in our present study, in any of the patients with stage 1 prolapse, detrusor pressure was not >100 cmH_2O and in 3.30% of patients with stage 2 prolapse and in 1.60% of patients with stage 3 prolapse pdetQmax >100 cmH_2O.

Pressure flow studies may be inadequate to reveal this distinction in patients with both obstruction and contractility disorder. There is also an ambiguous group lacking final decision about their status. In 1999, Abrams *et al* have suggested bladder outlet obstruction index and bladder contractility index concepts in their publication[32]. BCI and BOOI are formula used for males. There is no such index for females; however, when evaluated with these parameters, there was no statistically significant difference in this study between BOOI and BCI averages. In our study, as stage increases, the rate of weak bladder contractility also increases, though insignificantly. When detrusor leak point pressure (DLPP) is > 40 cmH2O, upper urinary tract is at risk[33]. In our study, as stage of prolapse increases this pressure also increases, though insignificantly. It can be concluded from our study that in cases with advanced stage anterior vaginal wall prolapse, we have to be vigilant about probable upper urinary tract disorders due to DLPP increase.

CONCLUSION

This study designed to evaluate urodynamic study results of patients with anterior vaginal wall prolapse; in 66% of stage 3 prolapse, some type of incontinence was observed. Additionally it was also observed, that bladder volume, capacity, compliance and residual urine rates also increased as the stage of prolapse increased. These results are similar to other studies in the literature that the bladder sensation decreases in patients with POP along with increase in POP stage; thus calls for vigilance about post-op voiding dysfunction in patients with anterior wall prolapse. Thus, the urodynamic studies are still the gold standard in evaluation of urinary dysfunction. In order not to encounter unexpected consequences, routine urodynamic evaluations should be done before POP treatment procedures.

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Original Article

Clinical Comparative Analysis of Neonatal Scalp Vein and Axillary Vein Catheterization

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ABSTRACT

Objective: To compare the clinical effectiveness and safety of axillary vein catheterization (AVC) and scalp vein catheterization (SVC) in the neonatal intensive care unit (NICU).
Design: Retrospective study
Setting: The Central Hospital of Xinxiang, China
Subjects: One hundred and fifteen cases from the NICU were enrolled from June 2012 to June 2013.
Interventions: Fifty-four patients underwent AVC and 61 underwent SVC.
Main outcome measure(s): Catheter-related bloodstream infection, catheter obstruction, ectopia, phlebitis, and local leaking
Results: No significant difference between groups was observed for catheter related bloodstream infection (SVC: 4.4%, AVC: 3.7%, p = 0.56) and catheter obstruction (9.8% vs. 9.3%, P = 0.87) between the two catheterization methods. However, the rate of catheter ectopia, phlebitis and leaking in SVC were significantly higher than those for AVC (18.0% Vs. 3.7%, p = 0.02, 18.0% Vs 3.7%, p = 0.02 and 16.4% Vs. 3.7%, p = 0.03, respectively).
Conclusions: Although both SVC and AVC could be the choice for intravenous infusion in the NICU, AVC was safer than SVC in newborn infants.

KEY WORDS: intravenous infusion, neonatal peripheral vessels , newborns

INTRODUCTION

Some newborn children need intravenous infusions of a nutritious solution, as well as certain stimulant medications, for a very long time[1]. Due to the congenital shortage of neonatal peripheral vessels, leakage can easily occur, leading to such care complications as phlebitis, skin necrosis, infections, and others[2]. In recent years, scalp vein catheterization (SVC) has reduced the workload of nurses, especially when caring for critically ill children. SVC can facilitate the rescue of critical newborns, save time, and improve the salvage rate[3]. SVC has gradually become a common infusion method in pediatrics, because it solves the problems of delivering fluid replacement and medication, and reduces the rate of complications such as puncture failure, phlebitis, and indwelling needle abscesses[4]. However, it was found in clinical practice that the complication rate of SVC is affected by multiple factors, and it is likely to causing phlebitis[5]. Although SVC has many advantages, in fact, the problems caused by intravenous catheterization still need some thinking and research[6].

In an effort to address the problems mentioned above, in this study, we propose using axillary vein catheterization (AVC) technology, and we compared it to SVC to see if it could improve the effects of neonatal intravenous catheterization and reduce the complications. AVC infusion has been shown to be safe[7]. As a rescue infusion pathway for critically ill newborns, compared with catheterization in other body parts, AVC has been reported to be superior in the puncture success rate, retention time, and complication rate[8]. In an investigation of AVC in neonates, the adverse reactions were fewer, and the minor-lateral position, with the arm outer-extending degree at 110 - 145, had a high puncture success rate[9]. When rescuing critically ill newborns, AVC infusion appears to be safe, and the complications are fewer; thus, it could be used as the preferred intravenous catheterization choice for newborns in the neonatal intensive care unit (NICU).

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SUBJECTS AND METHODS

In clinical care, the neonatal intravenous infusion is an important therapeutic procedure, as well as an important nursing technique[10]. The intravenous indwelling needle, also known as the trocar, is made of advanced biological materials. It was first applied in the clinics as a replacement for scalp puncture in 1958, and was widely used in the United States and Europe 30 years ago[11]. Most healthcare providers have been using the scalp vein and limb superficial vein for puncturing catheterization of neonatal patients, but these are prone to leakage and phlebitis, especially for the infusion of hypertonic liquids and vasoactive drugs, because the stimuli to the blood vessels during the infusion is very intense[12].

Our division used vein catheterization for 136 newborns in the NICU of our hospital from June 2012 to June 2013, among whom 13 cases of treatment abandonment were excluded, and eight patients died. The remaining 115 patients were discharged after recovery, so they were enrolled into this study. The detailed information of the newborns were retrospectively analyzed, to compare the relevant outcomes that occurred during scalp versus axillary vein catheterization.

Subjects

Our department performed 136 cases of vein catheterization on NICU newborns from June 2012 to June 2013. After excluding 13 cases of treatment abandonment and eight patients who died, the 115 patients who were discharged after the treatment were included in this study. The detailed information of these children was retrospectively analyzed to compare the outcomes of SVC to those of AVC. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Central Hospital of Xinxiang. Written informed consent was obtained from all participants' guardians.

Scalp vein catheterization

Skilled nurses performed the vein catheterizations. The needles were disposable Intima-11 intravenous needles (Becton Dickinson Medical Devices Co., Ltd., Suzhou). According to the distributions of blood vessels, the puncture sites chosen were thicker vessels such as the posterior auricular vein, superficial temporal vein, frontal median vein, and frontal horn branch. First, the hair in an approximately 6 cm diameter area at and around the blood vessel was shaved, then 0.25% povidone-iodine was used to disinfect the skin puncture site, followed by 75% alcohol de-iodination and air-drying. During the puncture, the heparin cap was inserted into the scalp vein to drain the air, so that adhesions between the casing and needle core could be prevented and then the regulator was closed. The right hand held the needle wing, and formed a 15 - 25° angle towards the scalp, then inserted the needle. The insertion was slow and the blood return was observed. When the needle core was withdrawn, the outer tube was inserted, until it was all placed into the tube. After observing that the infusion was smooth and had no extravasation, the needle was fixed with a transparent applicator, with the injection time noted on the tape, and the extension tube fixed on the child's head.

Axillary vein catheterization

The catheterization was performed by the same skilled nurses, and the needle was the same type as that used for SVC. The patient was in the supine position, with one arm straightened outwards to fully expose the armpit. The axillary vein connects to the end of the subclavian vein, and the site where it intersects with the clavicle is 65.7 + 6.2 mm away from the collarbone inner end[13]. Starting from the intersection of the clavicular 2/5 inner side and 3/5 outer side, the diameter is 12.3 + 0.2 mm. It is located underneath the axillary artery. After feeling for the pulsatility of the axillary artery, the needle was inserted under the armpit 0.3 cm below the site where the most obvious beat is felt. When the pulsatility was unclear, the needle was inserted at the intersection of 0.2 - 0.4 cm to the armpit midpoint and 1.0 - 1.2 cm under[14]. Conventional disinfection was then performed at the puncture site. The left hand of the operator held the upper arm of the child to tense the lower skin, then slowly inserted the needle 0.5 - 1 cm beneath the puncture point with an angle of 10 - 15°. When the blood return was seen, the needle was also inserted 0.1 - 0.2 cm, and then the needle core was withdrawn. The soft core was then sent into the axillary vein, to ensure the indwelling needle stayed inside the vessel. The saline syringe was connected, and when the blood could be withdrawn smoothly, the saline was injected to seal the tube, and 3 M transparent applicator was used for fixation.

Post-catheterization nursing

The nursing was performed according to conventional venipuncture and extubation nursing procedures. Tube sealing liquid was used for plugging, and the assessments were performed in accordance with the venous catheterization record. The drugs, highly concentrated nutritious solutions, high sugar solutions (glucose concentration >12.5%), and high osmotic pressure solutions (osmotic pressure >850 mOsm/L) were all infused through the intravenous catheter. The axillary vein is relatively coarse, close to

Table 1: SVC, AVC clinical features of comparison.

Puncture	Cases	Birth weight	Gestational age	Baby Boy		Puncture time of age	Indwelling time	Liquid infusion time
		(x ± s, g)	(x ± s, W)	Cases	PCT (%)	(x ± s, d)	(x ± s, d)	(x ± s, d)
SVC	61	1340 ± 270	30.5 ± 2.3	40	65.6	8.2 ± 5.8	2.2 ± 1.2	25.8 ± 14.3
AVC	54	1340 ± 680	29.9 ± 2.5	29	53.7	7.5 ± 6.2	2.5 ± 1.8	30.2 ± 19.3
T or x^2		0.08	1.15		1.70	0.29	0.98	1.40
P - value		0.94	0.25		0.25	0.77	0.33	0.16

large blood vessels. If the infusion is not smooth, the infusion tube should not be squeezed to prevent small blood clots from being forcefully squeezed into the blood circulation where they can form a thrombosis[15].

Indwelling time and extubation

The length of time the catheter was left in place depended on the decisions of the neonate-professional attending physicians and nurses of the intravenous infusion group, according to the clinical situation. Extubation was performed immediately when catheter-related infections and other related complications occurred.

Vein catheterization-related complications

The diagnostic criteria for catheter-related bloodstream infections (CRBSI) were as described in the literature[16], namely that bacterial colonies were cultured from the peripheral blood during the catheterization and within 48 h after the extubation. Phlebitis was defined as mechanical or chemical, not related to infections, exhibiting a red streak from the puncture point and along the catheter, and accompanied by induration. Catheter blockage was defined as when the infusion pump alarm went off, the infusion could not continue, and when the catheter was withdrawn, there was no blood return. Oozing was defined as when the fluid exosmosed into the tissue space, causing local swelling and pain.

Statistical analysis

The SPSS 11.5 software package was used for the statistical analysis. The categorical data were expressed by the frequency and rate. The intergroup comparison used a non-parametric test and Fisher's exact test; the normally distributed measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± s), and the intergroup comparison used the two-sample t test, with $P < 0.05$ considered to indicate statistical significance.

RESULTS

Clinical features

Among the 115 patients, 83 were very-low or ultra-low-birth-weight children, and 32 cases were diagnosed as low-birth-weight children, smaller-than-gestational-age children, or with neonatal hypoglycemia. SVC was performed on 61 cases, and AVC on 54. The birth weight, gestational age, sex, age when the puncture catheterization was performed, catheterization duration, and intravenous infusion time were not significantly different between the groups (Table 1).

Catheterization-related complications

There was no statistically significant difference in the rates of CRBSI between the two groups. The pathogens cultured from the blood included *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus* and coagulase-negative *staphylococci*. The catheter displacement rate, phlebitis, and exudation rate of the SVC group were statistically, significantly higher than those of the AVC group (Table 2).

DISCUSSION

Among the 115 cases, the rates of CRBSI of the two groups had no statistically significant difference, while the catheter displacement rate, phlebitis, and exudation exhibited a statistically significant difference (Table 2). The catheter displacement rate of the SVC

Table 2: SVC, AVC situation is related complications

Puncture	Cases	CRBSI		Catheter blockage		Catheter displacement		Phlebitis		Oozing	
		Cases	PCT (%)	Cases	PCT (%)	Cases	PCT (%)	Cases	PCT (%)	Cases	PCT (%)
SVC	61	3	4.4	6	9.8	11	18.0	10	16.4	8	13.1
AVC	54	2	3.7	5	9.3	2	3.7	2	3.7	1	1.9
P-value		0.56		0.87		0.02		0.03		0.04	

CRBSI : catheter-related bloodstream infections, PCT: procalcitonin

group was significantly higher than that of the AVC group, which is likely related to the fact that the scalp vein wall is thin, easily flattened, easily slides, and the branches are mostly net-like. The return of blood appears as impulse-like, and the resistance is greater when pushing the medications. While the axillary vein has fewer branches, it is thick, straight, and easily punctured. Therefore, the rate of axillary vein displacement is significantly lower than the scalp vein. The phlebitis rate of SVC was significantly higher, and this is related to the fact that the lumen diameter of the scalp vein is small, with more branches, thus the resistance to fluid infusion is higher, and the vascular intima can be easily injured. At the same time, the vascular intima can prevent liquid leakage. Meanwhile, the fluid will damage the endothelial cells, exposing the subendothelial layer. The stimulation will thus induce inflammatory reactions, and the endothelial cells may release negative charges to prevent the platelets from adhering to the vessel wall, possibly leading to the formation of a thrombosis[17].

We require a change in our conceptualization of venipuncture catheterization. People habitually think that AVC is used only when SVC failed, and because it is located in the armpits, sweat or other secretions could easily cause contamination, thus the risk of infection is increased. Intravenous infusion is an important way for neonates to receive drug therapy and nutritional intake. Clinical studies have proven that axillary vein puncture can avoid and reduce the stimulation of the blood vessels by specific drugs, reducing the pain caused by repeated punctures[18]; therefore, it is suitable for 24 h continuous infusion. The osmotic tolerance of the axillary vein is similar to that of the central vein, and therefore preterm children that need intravenous nutrition can achieve very good results by axillary vein infusion[19]. The results of AVC for preterm children are better than limb-intravenous catheterization, are conducive to clinical medication and rescue, can reduce the incidence of phlebitis, alleviate the children's suffering, and the drugs can be accurately, quickly, and safely delivered for therapeutic purposes[20].

AVC did not increase the infection rate in our study. It appears to be the ideal place for indwelling catheters because it is easy to achieve fixation and has a reduced displacement rate. Because of the postural characteristics of newborns, namely the upper extremity is normally extended upwards and exhibits flexion, and the fact that the axillary vein is thick, AVC can avoid the occurrence of phlebitis and oozing. AVC cannot easily cause significant damage and scarring. However, SVC can easily lead to scarring when exudation and phlebitis occur, leading to dissatisfaction, complaints, or compensation disputes from the patients' families. Thus, the ideas should be changed, and we should consider AVC as the preferred method. Research has shown that AVC is safe and effective. Compared with SVC, its overall complications are fewer; therefore, AVC is a better choice for newborns.

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Original Article

Comparison of Pulmonary Hydatid Cysts between Men and Women

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ABSTRACT

Objective(s): To discuss the features of pulmonary hydatid cysts in male and female patients in terms of clinical, radiological, and surgical approaches
Design: Retrospective study
Setting: Thoracic surgery clinics of two universities in Turkey
Subjects: Comparison of pulmonary hydatid cysts between men and women
Intervention(s): Over the last 10 years, surgery was performed on 84 patients with pulmonary hydatid cysts (62 female and 22 male).
Main outcome measure(s): The patients in both groups were analyzed according to clinical, radiological, surgical, and postoperative characteristics.
Results: In this study, the number of female patients who underwent surgery due to pulmonary hydatid cysts was significantly higher than males. In our study, cyst diameter was found to be greater in men than women (respectively, 7.018 cm and 4.560 cm; p = 0.001). When women and men were compared with respect to the rate of total complications, they were found to be higher in men than in women (p = 0.043). Length of hospital stay after surgery was also longer in men (15.29 d) than in women (6.90 d; p = 0.0001).
Conclusion(s): In our study, cyst diameter was found to be greater in men than women. Perhaps it may be related to lung and thorax volume being 20 - 25% smaller in women than in men. In order to reveal the differences between women and men for pulmonary hydatid cysts, there is a need for studies covering both large numbers of cases and large endemic areas.

KEY WORDS: hydatid disease, incisions, lung cyst, surgery, techniques

INTRODUCTION

Hydatid cysts, which are formed by the larval form of *Echinococcus granulosus*, are a serious public health problem especially in African and Middle Eastern countries. The adult form develops in the intestines of dogs and eggs are excreted with the feces. When people eat food contaminated with feces, hydatid cysts may develop in the liver, lung, brain, heart, bone, skeletal muscle, kidney, spleen, and other tissues. Clinical manifestations of hydatid cysts depend on the localization and diameter of the cyst. The incidence of hydatid cysts is 2/100,000 in Turkey, an endemic region for the disease[1]. Previous findings on age-related differences in this disease have directed us to seek an answer to the question "Is there a difference for gender?" For this purpose, 84 cases of pulmonary hydatid cysts, including 62 female and 22 male patients who underwent surgery during the last 10 years, were retrospectively reevaluated according to their clinical, radiological, and surgical features.

MATERIAL AND METHODS

The files of 90 pulmonary hydatid cyst patients who had been hospitalized and treated over the last 10 years in the Thoracic Surgery Clinic of Meram Medical Faculty, Konya Necmettin Erbakan University, Turkey, and the Thoracic Surgery Clinic of the Faculty of Medicine, Bozok University, were retrospectively reevaluated.

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All the participants were fully informed about the aims of the study and permission was obtained from patients, where appropriate. An ethics committee (Institutional Review Board) gave approval for the study to take place; it was conducted according to the Declaration of Helsinki as revised in 2000.

Six patients who refused treatment and were discharged, were excluded from the study. The remaining 84 cases were divided into two groups; female patients (n = 62) and male patients (n = 22). Clinical, radiological, and demographic characteristics, treatment methods, and the follow-up of cases were evaluated. Initial patient diagnosis was usually made following a chest X-ray. Subsequently, a thoracic CT was performed for a detailed assessment and abdominal ultrasound was used for abdominal scanning. An MRI was also performed on some specific patients when a diagnosis could not be made by thoracic CT. All patients were treated surgically; underwent selective double-lumen intubation in order to deflate the lung during surgery and prevent lung contamination in cases of cyst explosion. Thoracotomy was usually performed, or synchronous or metachronous bilateral thoracotomy for pulmonary cysts. Phrenotomy was performed with right thoracotomy in four patients who had simultaneous hydatid cysts in the liver and lungs. During surgery, intact cysts were supported by gauze pads soaked with hypertonic saline and thus infection of surrounding tissues was prevented. A thick needle was then inserted into the cyst and its contents aspirated. Subsequently, cystotomy was performed at the place of injection, the remaining liquid in the cyst was aspirated, and the germinative membrane was removed with the help of a clamp. The contents of the cyst were then irrigated with 1% povidone-iodine, the lung was inflated, and bronchial leakages were detected. After all bronchial openings were closed with absorbable sutures, the cavity area was quilted, starting from the deepest point. Surgical resection was performed in some cases of hydatid cysts that caused irreversible changes to the lungs. Left pneumonectomy had to be performed in a case with a hydatid cyst in the pulmonary artery. Simultaneous intervention was performed using the thoracophrenotomy method in four patients with hydatid cysts in the right lung and liver dome. After the omental flap was placed into the remaining residual cavity area within the liver, and a subdiaphragmatic drain was placed under the diaphragm, the diaphragm was closed. A female patient with a hydatid cyst in the left ventricular wall of the heart and bilateral lung cysts underwent a sternotomy and her heart was attached to a pump while the cyst in the left ventricular wall was firstly operated upon, followed by opening of the bilateral mediastinal pleura when cysts in both lungs were addressed. A cystotomy capitonnage process was carried out with a single-port video thoracoscopic surgery (VATS) incision in a 42-year-old woman who had peripheral hydatid cysts in the upper lobe of the right lung.

Of three male patients with bleeding from postoperative drainage line, one patient was submitted to re-exploration, two patients were followed conservatively and bleeding was controlled in all cases promptly. Complaints related to spastic colon developed in two male patients and they were treated conservatively and recovered without any complication. Postoperative contralateral pneumothorax developed in one female patient was treated with tube thoracostomy. Suppuration on the incision line developed in two female patients. Their suppurations were evacuated, the sutures were released step by step and dressed with rifocine vials. The patients recovered without any complication. Prolonged air leakage was managed with long-term drainage and treated without air leakage at follow-up. Albendazole (10 mg/kg/day) treatment was administered to all patients for three postoperative months in order to prevent recurrence.

RESULTS

The mean age for patients was 43.55 y for females and 36.50 y for males. While the mean number of lung cysts was 1.79 per case for females, it was 2.73 for males. Average cyst diameter was 4.56 cm in women and 7.01 cm in men, this was statistically significant (p = 0.001). There was no significant difference between females and males in respect to the number of ruptured cysts (respectively, 0.68 and 0.73, p = 0.671; Table 1). While the most common symptom was coughing in women and men (48.4% and 36.4%, respectively), the second most common symptom was chest pain in women (22.6%). The second and third most common symptoms for men were shortness of breath and hydoptysis, in

Table 1: Demographic distribution of the study groups in cases of pulmonary hydatid cysts

Demographic distribution of the study groups	Gender	n	Mean	Standard deviation
Age (y)	Female	62	43.55	17.848
	Male	22	36.50	23.658
Number of pulmonary cysts	Female	62	1.79	1.427
	Male	22	2.73	4.662
Diameter of cysts (cm)	Female	62	4.56	2.0992
	Male	22	7.018	3.4356
Number of ruptured cysts	Female	62	0.68	0.696
	Male	22	0.73	0.631
Number of intact cysts	Female	62	1.06	1.172
	Male	22	1.73	4.026

equal proportion (27.3%). Other symptoms in both groups were hemoptysis, nausea, vomiting, fever, and syncope ($p < 0.001$; Table 2). For women, cysts were present in the right lung (58.1%), in the left lung (35.5%), and bilaterally (6.5%); for men, it was 45.5%, 45.5%, and 9.1%, respectively. There was no significant difference between men and women with respect to the distribution of cysts ($p = 0.590$; Table 3). While there was an isolated lung cyst in 66.1% of female cases, this rate was 63.6% in men. The most common localization of cysts after the lungs was in the liver in both sexes. There were other extrapulmonary localizations such as the mediastinum, heart, and kidney; with the exception of the liver, there was no difference between sexes in terms of the extrapulmonary localization of cysts ($p = 0.132$; Table 4). The most common type of surgery performed was cystotomy and capitonnage in both sexes. After this, cysts in the lungs and liver were operated on simultaneously with a thoracophrenotomy approach in four female patients. Lung resection was performed in seven female patients and there were no resections in male patients. Bilateral lung cysts were operated on simultaneously by bilateral thoracotomy or sternotomy in three female patients and one male. Surgery was performed using bilateral thoracotomy with a 1-month interval in one female and one male patient ($p = 0.020$; Table 5). Postoperative hemorrhage occurred in three male patients, spastic colon in two males, and prolonged air leakage in two males; in females, postoperative contralateral pneumothorax took place in one patient, prolonged air leakage in three patients and wound site suppuration in two patients. When men and women were compared for rates of total complications, this was found to be higher in men ($p = 0.043$; Table 6). Postoperative drainage duration of the male patients was significantly higher compared to that of the female patients (13,61 days Vs. 5,43 days respectively $p < 0.05$). When women and men were compared for length of hospital stay after surgery, it was found to be longer in men (15.29 d and 6.90 d, respectively $p = 0.0001$; Table 7).

Table 2: Distribution of symptoms according to gender in cases of pulmonary hydatid cysts

Symptoms	Sex		Total n (%)
	Female n (%)	Male n (%)	
Cough	30 (48.4)	8 (36.4)	38 (45.2)
Chest pain	14 (22.6)	2 (9.1)	16 (19.0)
Shortness of breath	2 (3.2)	6 (27.3)	8 (9.5)
Hydoptysis	4 (6.5)	6 (27.3)	10 (11.9)
Other	12 (19.4)	0	12 (14.3)
Total	62 (100)	22 (100)	84 (100)

Table 3: Distribution of cyst localization according to gender in cases of pulmonary hydatid cysts

Distribution of cyst localization	Sex		Total n (%)
	Female n (%)	Male n (%)	
Right lung	36 (58.1)	10 (45.5)	46 (54.8)
Left lung	22 (35.5)	10 (45.5)	32 (38.1)
Bilateral	4 (6.5)	2 (9.1)	6 (7.1)
Total	62 (100)	22 (100)	84 (100)

Table 4: Localization of extrapulmonary cysts according to gender in cases of pulmonary hydatid cysts

Localization of extrapulmonary cysts	Sex		Total n (%)
	Female n (%)	Male n (%)	
Anterior mediastinum	2 (3.2)	0	2 (2.4)
Heart, pulmonary artery	2 (3.2)	0	2 (2.4)
Liver	17 (27.4)	6 (27.3)	23 (27.4)
Kidney	0	2 (9.1)	2 (2.4)
No extrapulmonary cyst	41 (66.1)	14 (63.6)	55 (65.5)
Total	62 (100)	22 (100)	84 (100)

Table 5: Classification of surgical methods according to gender in cases of pulmonary hydatid cysts

Surgical methods	Sex		Total n (%)
	Female n (%)	Male n (%)	
Cystotomy + capitonnage	47 (75.8)	16 (72.7)	63 (75.0)
Lung + liver thoracophrenotomy	4 (6.5)	0	4 (4.8)
Resection	7 (11.3)	0	7 (8.3)
Bilateral operation	4 (6.5)	6 (27.3)	10 (11.9)
Total	62 (100)	22 (100)	84 (100)

Table 6: Distribution of different postoperative complications according to gender in cases of pulmonary hydatid cysts

Postoperative complications	Sex		Total n (%)
	Female n (%)	Male n (%)	
Bleeding	0	3 (13.6)	3 (3.6)
Contralateral pneumothorax	1 (1.6)	0	1 (1.2)
Spastic colon	0	2 (9.1)	2 (2.6)
Prolonged air leakage	3 (4.8)	2 (9.1)	5 (6.0)
Suppuration of wound site	2 (3.2)	0	2 (2.4)
None	56 (90.3)	15 (68.2)	71 (84.5)
Total	62 (100)	22 (100)	84 (100)

Table 7: Postoperative hospital length of stay (days) in patients treated for pulmonary hydatid cysts

Postoperative length of stay	n	Mean	Standard deviation
Male	14	15.29	5.553
Female	70	6.9	2.127

DISCUSSIONS

The incidence of hydatid cysts in men and women varies according to age range and from region to region. Professional groups appear to have an impact on these regional differences[2-5]. In a previous study, while the ratio of male and female patients was found to be equal in adults, it was stated that the ratio in male children was three times higher than that in female children[3]. In a group of adults aged 21–30 years, the incidence of cysts was found to be higher in women (58.1%) than in men (41.9%). In this study, it was also noted that the incidence of hydatid cysts in women and men showed a difference among cities. All of these differences in gender and the incidence of hydatid cysts are reported to be associated with the social and cultural structure of the region[4-5]. In our study, 62 (73.81%) patients were female and 22 (26.19%) patients were male. While the majority of female patients were housewives from rural areas, the majority of male patients were agricultural workers.

Previous studies have stated that perforation and postoperative complications increase with increasing cyst size[5]. No correlation has been reported between cyst size and pressure within lung cysts. Furthermore, it was stated that pressure within the cyst increases with increasing size of liver cysts, and it was considered that this pressure difference between the lung and liver could be related to lung elasticity[1]. There are studies indicating that cyst diameter is greater in children than adults because the elasticity of the lung is higher in children[3-6]. A similar correlation has not been reported between men and women. In our study, cyst diameter was found to be greater in men than women (respectively, 7.018 cm and 4.560 cm; $p = 0.001$). We did not find any morphological description that could explain this situation. Perhaps it may be related to lung and thorax volume being 20 - 25% smaller in women than in men[7]. Moreover, it was stated that the sex hormones estrogen and progesterone in women have features such as negative effects on the smooth muscle in the respiratory system[8], but it is unknown whether this negative effect has a connection with cyst growth in the lungs. The difference in cyst size between sexes as found in our study should be clarified during larger trials in the future.

The most common symptoms of pulmonary hydatid cysts are coughing, mucopurulent sputum, chest pain, hydoptysis, hemoptysis, and fever. It was stated in a previous study that while hemoptysis is more common in adult patients, there is no difference in terms of other symptoms[6]. However, in the literature there has been no comparison in terms of symptoms of pulmonary hydatid cysts between males and females. In our study, the most common symptom in women and men was found to be coughing (respectively, 48.4% and 36.4%), and this is in harmony with the literature. While the second most common symptom in women was chest pain (22.6%), in men it was hydoptysis and shortness of breath in equal proportions (27.3% and 27.3%, respectively).

While cysts are most commonly localized in the lungs in pediatric patients, they are mostly localized in the liver of adult patients[4]. It is also known that pulmonary hydatid cysts are most commonly found in the right hemithorax, more specifically in the right lower lobe. The most common extrapulmonary localization is the liver[1,3,6]. In our study, total lung cysts (women and men) were placed as 54.8% in the right lung, 38.1% in the left lung, and 7.1% bilateral. For women only, cysts were observed in 58.1% of right lungs, 35.5% of left lungs, and 6.5% bilaterally; in men they were observed in 45.5%, 45.5%, and 9.1%, respectively. The most common extrapulmonary localization was the liver in both genders (27.4% and 27.3%, respectively). Excepting the liver, cysts were observed in the anterior mediastinum in two female patients, in the left ventricle wall of the heart in one female patient, and within the pulmonary artery in one female patient.

An intact cyst is seen as a sharply demarcated and homogeneous, rounded radiopacity in radiographs. Various radiographic tables such as lotus flower sign, hydroaeric level, crescent sign, meniscus sign, pneumonic infiltration around the cyst, and pleural fluid depending on the opening of the pleura can be seen in pulmonary hydatid cysts. Meniscus (crescent) signs are visible in chest radiograms, produced by the entry of air into the space between the endocyst and pericyst. Endocysts can be completely expectorated in chronically infected cysts, and a hydroaeric levelling and a rather thick pericyst wall are formed within the cavity. Such a hydatid cyst cannot be separated from a pyogenic abscess and malignancies[1-3]. The presence of cyst membranes and loculated fluid fields in some complicated hydatid cysts, viewed on MRI scans, may be demographic diagnostic. Abdominal ultrasound and CT scans should also be made in order to identify cysts localized in the abdomen[3,9]. Because of the diagnostic value of laboratory tests such as the Casoni intradermal test, serological tests for hydatid cyst antibodies and the number of eosinophils are only used in around 50% of cases; they are not used routinely by many clinics[1,6]. In our cases, we routinely used chest X-rays, CT scans, and abdominal ultrasound. We also used MRI in pericardial, pleural, and diaphragmatic areas and in cases of complicated hydatid cysts. We did not routinely perform serological tests because of their low diagnostic value.

The main treatment for patients with pulmonary hydatid cysts is surgery. Posterolateral thoracotomy,

bilateral thoracotomy, and sternotomy are the most preferred incision methods. Bilateral thoracotomy can be applied simultaneously or with an interval of three weeks, depending on the clinical condition of the patient. This is not a preferred method, except for cysts accompanied by mediastinal or cardiac hydatid cysts due to the risk of infecting the mediastinumin. With developments in minimally invasive surgical procedures in recent times, single-port VATS has become a common surgical procedure for pulmonary hydatid cysts[10]. We also performed a cystotomy capitonnage operation with a single-port VATS incision in a 42 y-old female patient who had peripheral hydatid cysts in the upper lobe of the right lung. This aimed to eliminate the parasite using surgical treatment, to prevent cyst rupture during surgery and subsequent propagation, and to resolve the remaining cyst cavity by protecting pulmonary tissue. Parenchyma-conserving surgery methods (enucleation, cystotomy-capitonnage, pericystotomy, and wedge resection) are all used. If the destruction of a lobe is more than 50% and irreversible fibrosis has developed, then resection should take place [11]. In our study, the most common surgery was cystotomy capitonnage in both women and men (75.8% and 72.7%, respectively). While resection was performed in seven female patients (11.3%), it was not performed in male patients. Medical treatment consisting of albendazole or mebendazole is not a preferred practice due to the risk of rupture and anaphylaxis before surgery. Even though cyst contents are killed by medical treatment, there is a high risk of pneumonia and lung dilapidation because of cyst membranes remaining in the cavity[4,6]. Therefore, the main treatment for pulmonary hydatid cysts is surgery. Medical reatment is preferred to prevent recurrence after surgery. Our preference was for albendazole treatment in all patients for 20 days with 10-day breaks for three months postoperatively and simultaneous monitoring of liver enzymes in patients who underwent surgery.

Hydatid cyst surgery is not usually complicated, and morbidity and mortality rates are very low. The most common postoperative complications are bleeding, prolonged air leakage, pneumothorax, atelectasis, pneumonia, and empyema[11]. There was no significant difference with respect to the rate of postoperative complications between adults and pediatric patients[3]. In our study, the complication rate was found to be higher in men than women (respectively, 31.8% and 11.3%). Mortality was not observed in either group. Postoperative length of hospital stay was also correlated with the rate of postoperative complications; it was found to be higher in men (respectively, 15.29% and 6.90%).

The results of this study indicated that pulmonary hydatid cysts were more common in women than in men and cyst diameter was greater in men than in women. Inadequacies of our study related to the low number of cases and the collection of data from a narrow socio-cultural aspect. The differences in pulmonary hydatid cysts between men and women can be more clearly revealed by future studies, which should include a larger number of cases and a wider geographic area.

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Original Article

Interventional Bronchoscopy via Laryngeal Mask Airway (LMA) Under General Anesthesia in Children using Adult Flexible Bronchoscope

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ABSTRACT

Objective: To evaluate the safety and effectiveness using adult flexible bronchoscopy via laryngeal mask airway (LMA) under general anesthesia in children aged 2 - 5 years
Design: Retrospective study
Setting: Yuhuangding Hospital, Yantai, China
Subjects: The procedures of bronchoscopy were performed with an adult flexible bronchoscope via LMA under general anaesthesia. Indications and complications were analyzed, retrospectively.
Intervention(s) : Expanding the wide use of pediatric flexible bronchoscopy to diagnostic and interventional bronchoscopy
Main outcome measure(s) : Performed using SPSS17.0
Results: The indications for bronchoscopy included tracheal mucous plugs removal in 108 cases with pneumonia, tracheobronchial foreign bodies removal in 82 cases, endobronchial biopsy in 66 cases, bronchoscopic cryosurgery in 23 cases with tracheal granulation tissue formation after long-term endotracheal intubation, balloon dilatation in 11 cases with lobar bronchial stenosis and bronchoscopic management in 12 cases with traumatic tracheobronchial injuries. Complications were reported for 193 cases, with an overall complication rate of 63.9%. The incidence rate was highest in children aged 2 - 3 years, and decreased with age. Hypoxia and post bronchoscopy cough were the most complication in all patients. Acute hypoxia during bronchoscopy happened in 5 (1.6%) cases and was relieved quickly by intermittent withdrawal of the bronchoscope. Most post bronchoscopy cough without respiratory distress or hypoxia could be seen in 188 (62.3%) cases and resolved within four hours after inhalation of budesonide.
Conclusion: An adult flexible bronchoscope via LMA could be safely and effectively used for interventional bronchoscopy in 2 - 5 years old children with different kinds of the proximal airway diseases.

KEY WORDS: endotracheal intubation, hypoxia, lung diseases, respiratory distress, tracheal mucous plugs

INTRODUCTION

Flexible bronchoscopy is an important tool in clinical evaluating and management of pediatric airway and lung diseases[1,2]. The pediatric flexible bronchoscope (PFB) has a small diameter to allow direct visualization of more distal airways, and thereby PFB has a significant diagnostic value. In view of the rapid advances in this field of this study, common indications for pediatric bronchoscopy have extended over a spectrum of therapeutic interventions such as removal of foreign bodies, endobronchial biopsy, balloon dilatation and cryotherapy[3-7]. However, PFB has a smaller diameter of suction channel which lack of size-appropriate equipments to limit instrumentation capabilities for therapeutic and interventional application in younger children[6].

In contrast to PFB, the standard 4.9 mm adult flexible bronchoscope with 2.0 mm suction channel can be equipped with grasping forceps (for foreign bodies), balloon catheters, electrosurgical and laser attachments to perform the corresponding interventional procedures[8]. But the practice of traditional choice of the way to enter the airway of the pediatric bronchoscopy is nasal route[9], the 4.9 mm external diameter of adult FB allows it to be commonly used for children over six years old[1].

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The laryngeal mask airway (LMA) is a widely used device and method which used to control airway during many current surgical procedures[10]. When the LMA correctly placed, the LMA can establish a direct access to the lower airway, and thereby avoid the disadvantages of FB insertion via the nasal route. Several studies have shown that, according to age and weight, the use of an appropriate size LMA according to age and weight may facilitate bronchoscopy in infants and children[11-13]. An LMA size 2 or 2.5 which often be used in 2 to 5-year-old children has an inter diameter of 7.0 mm, and 8.4 mm can pass through a 4.9 mm adult FB easily without a significant increase in airway resistance[14]. Therefore, it is feasible in theory that a 4.9 mm adult FB is used via an LMA under general anesthesia in bronchoscopy for younger children who are aged 2 - 5 years.

In the present study, in order to evaluate the efficacy and safety of this interventional procedure for younger children, we reviewed our experience of using adult flexible bronchoscope for interventional bronchoscopy via LMA under general anesthesia in 302 cases of children aged 2 - 5 years over the last six years, in order to evaluate the effectiveness and safety of this interventional procedure for younger children. To our knowledge, the outcomes of this technique for children have not been reported previously in the otolaryngology, thoracic surgery, or interventional pulmonology.

SUBJECTS AND METHODS

Subjects

We reviewed 302 cases of pediatric FB procedures which were performed by adult flexible bronchoscopy via laryngeal mask airway under general anesthesia in children aged 2 - 5 years from January 2008 to December 2013 by the pediatric pulmonologists in Yuhuangding Hospital (a tertiary care facility, Yantai, China). The present study was approved by the Ethical Committee of Yuhuangding Hospital. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from the parents or guardians.

Procedures

FB was performed in a bronchoscopy room equipped with anesthesia apparatus, supplemented with oxygen, suction, nebulizer inhalation, emergency medication, and monitoring and resuscitation devices. All children with preoperative fasting for 6 hr were premedicated with intramuscular midazolam 0.1 mg/ kg^{-1} and atropine 0.02 mg/kg^{-1}. Blood pressure, heart rate, transcutaneous oxygen saturation, tidal volume and minute ventilation were monitored continuously throughout the procedure. Anaesthesia was induced via a facemask using sevoflurance 6 - 8% in 6 L/ min^{-1} of 100% oxygen. Once an adequate depth of anaesthesia was achieved, a size 2.0 or 2.5 LMA (inner diameter of 7.0 and 8.4 mm, respectively. Hangzhou Shanyou medical equipment Co. Ltd, Hangzhou, China) was inserted. Propofol intravenous infusion was then administered at a rate of 0.1 ~ 0.2 mg/ kg^{-1}/min^{-1}, oxygen was supplemented by an L joint connecting the proximal end of the LMA to the T-piece anaesthesia system. An adult flexible bronchoscopy (Olympus, P30, outer diameter 4.9 mm, inner diameter 2.0 mm. Olympus optical company, Tokyo, Japan) was inserted via the L joint. Topical anaesthesia of the vocal cords using 2 ml of 2% lidocaine solution via the suction channel of the bronchoscope was applied to prevent laryngospasm. If necessary, the ancillary instruments such as biopsy forceps, foreign body forceps, were introduced via the suction channel to complete the relevant bronchoscopy. At the end of procedure, propofol infusion was discontinued and the patient was supplemented with 100% oxygen until recovery from anesthesia. Bronchoscopy indications and complications were documented during and after the procedures.

Data analysis

Data analysis was performed using SPSS17.0. Descriptive statistics were used to characterize the available data. All measurement data are reported as mean ± standard deviation as appropriate. Analyses were performed on both the overall data as well as according to the defined age groups.

RESULTS

Subjects

Three hundred and two peadiatric patients including 128 boys and 174 girls with mean age of 3.2 ± 0.8 years successfully underwent adult flexible bronchoscopy via laryngeal mask airway under general anesthesia from January 2008 to December 2013. Of the 42 cases (age 2 - 3 years old, mean 2.5 ± 0.4 years) suspected of having distal bronchial foreign bodies. As the flexible bronchoscopy could not be inserted down the lower lobe bronchus, but the foreign bodies could be visualized from the distance. Only the

Table 1: Demographics

Age groups	N (%)	Age (years)	Male/ female ratio
2 - 3 years	101 (33.4)	2.5 ± 0.8	0.74:1
3 - 4 years	94 (31.1)	3.3 ± 0.9	0.61:1
4 - 5 years	107 (35.5)	4.2 ± 0.7	0.78:1
Total	302 (100)	3.2 ± 0.8	0.98:1

Table 2: Indications for bronchoscopy according to age group[1]

Indications	Age group			Total n (%)
	2 - 3 years n (%)	3 - 4 years n (%)	4 - 5 years n (%)	
Removing of tracheal mucous plugs	5 (4.6)	37 (34.2)	66 (61.2)	108 (35.7)
Removing of tracheobronchial foreign bodies	54 (65.9)	20 (24.4)	8 (9.7)	82 (27.2)
Endobronchial biopsy	18 (27.3)	20 (30.3)	28 (42.4)	66 (21.8)
Bronchoscopic cryosurgery for tracheal granulation tissue formation	15 (65.2)	6 (26.1)	2 (8.7)	23 (7.6)
Balloon dilatation for lobar bronchial stenosis	8 (72)	3 (27.3)	0 (0)	11 (3.6)
Bronchoscopic management for traumatic TBIs	1 (8.3)	8 (66.7)	3 (25)	12 (4.1)
Total	101 (33.4)	94 (31.1)	107 (35.5)	302 (100)

[1]Percentage reflect percent of bronchoscopies performed for a given indication within a specific age group

foreign body forceps could pass through the suction channel to get close to the foreign bodies and remove them successfully. Additional demographic data are listed in Table 1.

Indications

Primary indications for FB are shown in Table 2. The indications for bronchoscopy in this study included tracheal mucous plugs removal in 108 cases with pneumonia, tracheobronchial foreign bodies removal in 82 cases (peanuts in 45 cases, sunflower seeds in 18 cases, corn kernels in 10 cases and fruit seeds in 9 cases), endobronchial biopsy in 66 cases, bronchoscopic cryosurgery in 23 cases with tracheal granulation tissue formation after long-term endotracheal intubation, balloon dilatation in 11 cases with lobar bronchial stenosis and bronchoscopic management including determination of injury location and its extending, removal of blood clots using cryotherapy and then electric coagulation in 12 cases with traumatic tracheobronchial injuries (TBIs). Tracheobronchial bodies removal, bronchoscopic cryosurgery for tracheal granulation tissue formation and balloon dilatation for lobar bronchial stenosis were the most common indication for interventional FB in children aged 2 - 3 years, and both decreased thereafter. Tracheal mucous plugs removal, endobronchial biopsy and bronchoscopic management for traumatic TBIs were the most common indication in children aged 3 - 5 years.

Complications

Table 3 illustrates a description of specific complications reported. Complications were reported for 193 cases, with an overall complication rate of 63.9%. The incidence rate was highest in children aged 2 - 3 years, and decreased with age. No severe complications, including laryngospasm and massive bleeding, occurred during and after the procedure. Hypoxia and post bronchoscopy cough were the most complication in all patients. Five (1.6%) cases were subjected to acute hypoxia during bronchoscopy, which was relieved quickly by intermittent withdrawal of the bronchoscope. One hundred and eighty-eight (62.3%) cases went through post bronchoscopy cough without respiratory distress or hypoxia, which were all resolved within four hours after inhalation of budesonide.

DISCUSSION

Flexible bronchoscope (FB) is an important procedure for evaluating the pediatric airway, allowing a dynamic view from the trachea through the lower bronchi[15]. The FB may be done in conjunction with special procedures, such as bronchoalveolar lavage (BAL), brushing or biopsy of the bronchial mucosa, transbronchial biopsy, administration of drugs, endoscopic intubation[16-18]. Over the past few decades, evolution of the equipments has changed the profile of indications. Nowadays, pediatric bronchoscopy is more widely used in therapeutic interventions such

Table 3: Specific complications

Age groups	Any complication N (% of cases)	Specific complications				
		Hypoxia	Post bronchoscopy cough	Laryngospasm	Massive bleeding	Other[1]
2-3 years	89 (88.1)	3	86	0	0	0
3-4 years	72 (76.6)	2	70	0	0	0
4-5 years	32 (29.9)	0	32	0	0	0
Total	193 (63.9)	5	188	0	0	0

[1]Other: includes unspecified anesthesia-related complication, hypotension, bradycardia, and unspecified complications (one case each).

as removal of foreign bodies, endobronchial biopsy, balloon dilatation and cryotherapy[6]. In China, there are two types of standard pediatric bronchoscopes usually being used at most children's hospitals: 3.5 mm bronchoscope (outer diameter of 3.5 mm) and 2.8 mm bronchoscope, which are both with 1.2 mm suction channels, and lack of size-appropriate equipments for interventional bronchoscopy[7]. Due to its small caliber of the suction channel and lack of ancillary instruments, the application of interventional procedure has been limited in children. In contrast with PFB, the standard 4.9 mm adult flexible bronchoscopes have large channels (inner diameter of 1.2 mm) that permit suctioning of thick mucous plugs and have the capacity to complete almost any type of respiratory instruments[19]. Traditionally, the PFB conducted via nasal cavity under local anesthesia makes it almost impossible for younger children aged 2 - 5 years to perform bronchoscopy by adult FB via nasal cavity.

LMA is a widely used device and method to control airway during many current surgical procedures[10]. The LMA not only provides a totally patent airway to insert FB easily, but also avoids the possibility of trauma while passing the FB through the nose. If necessary, connection to a T-piece system provides a channel to ventilate and deliver oxygen to the patient when necessary. This is a particular advantage for children and patients who need respiratory interventions. It has been reported that flexible bronchoscopy could also be performed easily with this mask in children under sedation[10,14]. The size 2.0 or 2.5 LMA (inner diameter of 7.0 mm and 8.4 mm) was suitable for children aged 2 - 5 years according to the manufacturer's recommendation based on the children's weight[20], and can passed through a 4.9-mm adult FB easily without a significant increase in airway resistance[14].

Tan and Tan-Kendrick measured the right and left main bronchial diameters of children using the Fogarty catheter, the results showed that main bronchial diameter of the children aged 2 - 5 years were 4 - 8 mm (mean 6.0 mm)[21]. Therefore, the distal tip of 4.9 mm adult FB may go on to the bronchus via a LMA in most of the younger children. But in theory, the bronchial internal diameter needs to be at least 1 mm greater than the external diameter of bronchoscope. Therefore, the 4.9 mm FB can only be applied successfully to children aged 2 - 5 years with proximal bronchus lesions.

Tracheobronchial foreign body (TFB) impaction is a common occurrence in the pediatric population. A time series of Chinese children with tracheobronchial foreign body aspiration in 1991 ~ 2010 was observed. The results showed that 3149 patients were averagely 3.92 years old and children less than three years of age dominated the population at 81.1%[22]. A delay in the removal of a foreign body may increase morbidity and mortality, ranging from life threatening airway obstruction to recurrent infection and coughing or wheezing. Although the traditional instrument of choice for the management of TFBs in children is the rigid bronchoscope, distal airway foreign bodies posed a unique challenge because they may be angulated or deeply impacted in surrounding inflammation[23]. The rigid bronchoscopic technique may be unsuccessful[22,23]. The standard PFB can arrive at the foreign bodies that have migrated deeper into the subsegmental bronchi. However, the PFB cannot extract the foreign bodies because lack of ancillary instruments available to grasp the airway foreign bodies[24]. Hockstein and Jacobs reported a case of a 15-year-old girl with an airway foreign body (a tongue stud) in the right lower lobe. The foreign body could be visualized from a distance with 3.5 mm PFB, but when an endobronchial biopsy forceps was used, the view of the foreign body was obstructed by the forceps[25]. However, our study reported that the procedures were accomplished successfully by insertion of extraction instruments only in 46 children aged 2 - 3 years (mean 2.5 years old) with foreign bodies or thick mucus plugs, when the distal tip of FB couldn't arrive the third bronchus completely. In a word, the larger the bronchoscope, the better the image quality is[26]. Our data showed that the standard 4.9 mm adult FB could provide a significantly wider visual field during the procedure to remove almost any type of TFB in younger children.

Subglottic and tracheal stenoses are chronic inflammatory processes that can occurred as a result of several possible etiologies, most commonly as a complication of prolonged intubation. In recent years, with the advancement of instrumentation and technology, traditional tracheotomy has gradually been replaced by endoscopic management including cryosurgery, radial incisions and dilation[27]. Our study demonstrates successful management of subglottic and tracheal stenosis using the LMA for ventilation and surgical access with adult flexible bronchoscopy. These findings are consistent with previous repors[28]. Tracheobronchial injuries (TBIs) are rare but potentially life-threatening injuries. The traditional treatment for TBIs has been surgery, however, the first and most important priority of preoperational preparation is to ensure adequate airway, localize the injury and determine its extend[29]. Possible mostly conducted with flexible bronchoscopy[30,31]. In the present study, we conducted preoperative management successfully with adult flexible bronchoscopy in 12 children aged 2 - 5 years with TBIs.

Hypoxia during procedures due to decrease in the cross-section area available around the FB used in children is a worrying problems. Control ventilation by anesthesia apparatus may adequately overcome the added airway resistance caused by the FB in most of our patients. Only five children (mean 2.2 years old) developed hypoxia during procedures which were relieved rapidly by intermittent withdraw of the FB.

CONCLUSION

The present report shows that adult FB via LMA under general anesthesia is safe and effective for children aged 2 - 5 years. LMA has a larger diameter compared with transnasal route and permits the use of a relatively large adult FB without a significant increase in airway resistance, thus allowing adult diagnostic and interventional bronchoscopy for children aged 2 - 5 years with complex respiratory diseases to be successfully accomplished in this setting.

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Conflict of Interest: All authors declare that they have no conflicts of interest regarding this paper.

Declaration: The first two authors have equally contributed to this study

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Original Article

The Expression and Clinical Significance of Ferroportin and Hepcidin in Breast Cancer Patients

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ABSTRACT

Objective: To investigate the expression of ferroportin (FPN) and hepcidin in tissue from patients with breast cancer, and to evaluate the relationship between FPN and hepcidin expression and clinical features
Design: Retrospective study
Setting: Department of Hematology and Oncology in Taicang Hospital of Suzhou University, China
Subjects: Sixty-four Paraffin tissue blocks obtained from breast cancer patients, who underwent surgical resection during the period, January to December 2009.
Intervention : None
Main outcome measure: To test FPN and Hepcidin expression in breast cancer by using immunohistochemistry
Results: The positive expression rate of FPN was significantly higher in tissue from patients with the luminal A and luminal B types of breast cancer than in the poor prognosis group (75.8% Vs 41.99%; $p < 0.05$), while the positive expression rate of hepcidin was significantly lower (24.2% vs. 74.2%; $p < 0.001$). The rate of FPN expression was higher in the estrogen receptor (ER)-positive group than in the ER-negative group (77.4% Vs 42.4%), and the positive rate of hepcidin was lower (22.6%) compared to that of the hepcidin-negative group (72.7%). The expression of hepcidin and FPN was related to the molecular type, expression of the ER/progesterone receptor, and lymph node metastasis, but it was not related to anemia. The expression of hepcidin was negatively correlated with FPN expression ($r = -0.41$; $p < 0.01$).
Conclusion/s: The expression of hepcidin and FPN in breast cancer tissue was related to the endocrine type, lymph node metastasis, and T stage, but not anemia.

KEY WORDS: anemia, immunohistochemistry, lymph node metastasis, metabolism disorders, tumor

INTRODUCTION

Recent studies have shown that hepcidin was highly expressed upon stimulation of inflammatory mediators, especially interleukin 6, in patients with cancer[1-4]. Additionally, hepcidin has been shown to cause iron metabolism disorders through modulating the expression of ferroportin (FPN)[5,6], which results in anemia in patients[7-9]. However, recent reports have suggested that iron may function as a cofactor that contributes to the proliferation and differentiation of tumors[10,11]. Iron could affect tumor proliferation and metastasis by regulating the expression of various proteins involved in iron metabolism[12]. Recent studies have shown that iron metabolism disorders caused by hepcidin may play an important role in the development of breast cancer[11,13]. Therefore, we investigated the expression of hepcidin and FPN in tissue samples from patients with breast cancer associated with anemia. In addition, we evaluated whether there was a relationship between the molecular type of breast cancer and the expression of the estrogen receptor (ER)/progesterone receptor (PR), T stage, lymph node metastasis, biological characteristics, and Immunohistochemistry was performed to examine the expression of hepcidin and FPN in pathological tissue samples from patients with breast cancer, and the relationship between hepcidin and FPN expression and the molecular type, clinical features, and preoperative anemia was analyzed.

MATERIALS AND METHODS

Patient selection

Between January and December 2009, the paraffin blocks of 64 cases were generated from tissue samples

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obtained from breast cancer patients who underwent surgical resection and treatment in our hospital. The diagnosis was confirmed for all the patients through a pathological examination. The patients were not treated with chemotherapy or radiotherapy before surgery, and the median patient age was 55 years. Molecular typing was performed according to the 12th St. Gallen Consensus[14]. The molecular subtypes of breast cancer were identified by evaluating the expression of ER and PR, over-expression of human epidermal growth factor receptor 2 [HER2], and the Ki-67 labeling index on immunohistochemical analysis. The four subtypes are as follows: luminal A type (ER- and/or PR-positive, HER2-negative, Ki-67 index lower than 14%), 15 cases; luminal B type (ER- and/or PR-positive, HER2-negative, and Ki-67 index higher than 14%), 18 cases; HER2 over-expression type (ER- and PR-negative, HER2 strongly positive, and FISH-positive, 11 cases; and basal-like type (ER-, PR-, and HER2-negative), anemia was diagnosed when the hemoglobin levels were < 110.0 g/L. Fourteen patients were diagnosed with anemia and 50 were not. The TNM staging was consistent with the standards of the American Joint Committee on Cancer[15]. Of the total patients in the study, 21 had stage T1 and 43 had stage T2-T4 tumors. Twenty-six of 38 patients had lymphatic metastasis, two of 64 patients had distant metastasis, and 62 of 64 patients had no distant metastasis. As a control, we selected adjacent normal tissue from 15 patients with breast cancer. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Suzhou University. Written informed consent was obtained from all participants.

Immunohistochemistry

Immunohistochemistry was performed by using the StreptAvidin-Biotin Complex (SABC) staining system. Four consecutive sections, each with a thickness of 5 μm, were cut from the paraffin blocks and then incubated at 60 °C for 30 minutes. Dimethylbenzene, anhydrous alcohol, and different concentrations of alcohol were used to dewax the sections. They were then washed with water for two minutes. One section from each set was stained with hematoxylin and eosin to facilitate the pathological diagnosis according to the manufacturer's protocol (Wuhan Boshide Biological Engineering Co., Ltd., China. Produced by R&D Co., Ltd., Germany). The remaining four sections were stained by the SABC method. Phosphate-buffered saline instead of the primary antibody was used as a negative control.

Result determination

Brown or yellowish-brown staining of the cytoplasm and/or cytoplast was considered positive. Five visual fields were randomly selected at high magnification and then scored according to the staining depth of the tumor cells by using the following system: light yellow (1 point), tan (2 points), or brown (3 points). Based on the number of positive cells, a second score was assigned as follows: if the number of positive cells was less than 10%, (zero points), 11 - 25% (1 point), 26 - 50% (2 points), 51 - 75% (3 points), and greater than 75% (4 points). The two scores were then multiplied: zero was negative (-); 1 - 4 points was weakly positive, denoted as (+); 5 - 8 points was moderately positive, denoted as (++); and ≥ 8 points was strongly positive, denoted as (+++).

Statistical analysis

The data were analyzed using the commercially available SPSS statistical software, version 16.0 (IBM, Armonk, NY). Quantitative data were analyzed using χ^2 tests, and the Student-Newman-Keuls method was used to compare the groups. The Spearman rank-order correlation coefficient was applied, and $p < 0.05$ was considered statistically significant.

RESULTS

Hepcidin expression

The positive expression rate of hepcidin was 13.3% (2/15) in normal breast tissue and 48.4% (31/64) in breast cancer tissue. This difference was statistically significant ($p < 0.05$). The positive expression rates in tissue samples from stage T1 and stages T2–T4 patients were 33.3% (7/21) and 55.8% (24/43), respectively, and there was no significant difference ($p > 0.05$). Twenty-six of 64 cases have lymph node metastasis, and the positive expression rates in tissue from patients with or without lymph node metastasis were 65.4% (17/26) and 36.8% (14/38), respectively, which was significantly different ($p < 0.05$). The positive rates of hepcidin expression in luminal A and luminal B types compared to the HER2 over-expression and basal-like types were 24.2% (8/33) and 74.2% (23/31), respectively, and this difference was significant ($p < 0.001$). The positive hepcidin expression rates in patients who were ER-positive or ER-negative were 22.6% (7/31) and 72.7% (24/33) respectively, which was significantly different ($p < 0.001$) (Fig 1A, B; Table 1).

Ferroportin expression

The positive expression rate of FPN in normal breast tissue was 86.7% (13/15), while it was 59.4 (38/64) in breast cancer tissue; however, the difference was not significant ($p = 0.07$). The positive expression rates of FPN in tissue from patients with T1 and T2 - T4 stage cancer were 76.2% (16/21) and 27.9% (12/43), respectively, and the difference was significant ($p < 0.001$). The positive expression rates in tissue from patients

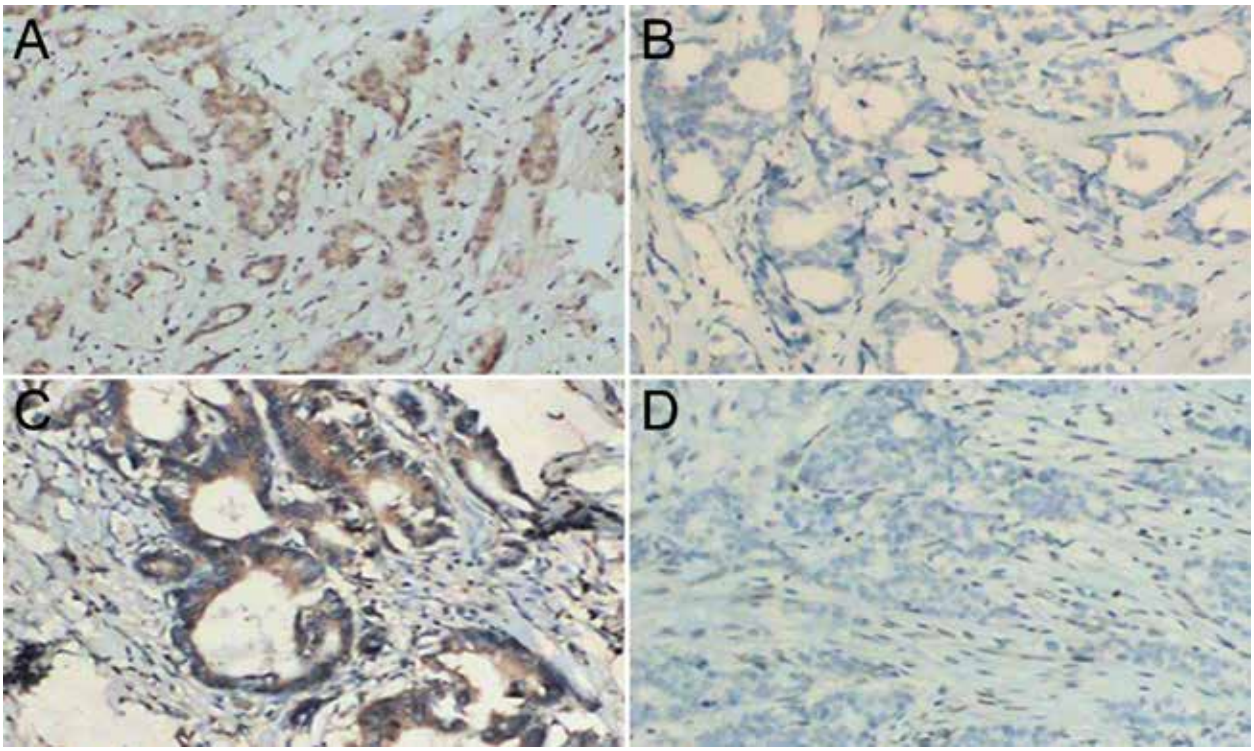

Fig 1: The expression of Hepcidin and FPN in breast cancer tissues (×400); **A:** Hepcidin (+); **B:** Hepcidin (-); **C:** FPN (+); **D:** FPN (-).

with or without lymph node metastasis were 42.3% (11/26) and 71.1% (27/38) respectively, and the difference was significant ($p < 0.05$). The positive rates of FPN expression in luminal A and luminal B types compared to the HER2 over-expression and basal-like types were 75.8% (25/33) and 41.9% (13/31) respectively, and the difference was significant ($p < 0.05$). The positive FPN expression rate in patients with ER-positive and ER-negative cancers were 77.4% (24/31) and 42.4% (14/33), respectively, and the difference was significant ($p < 0.001$) (Fig 1C, D; Table 1).

Correlation between ferroportin and hepcidin expression and anemia

Fourteen patients were diagnosed with anemia, three cases of luminal A type, two cases of luminal B type, three cases of HER2 over-expression type, and six cases of basal-like type. There was no clear correlation between the expression of FPN and hepcidin in breast

Table 1: Relationship between the expression of Hepcidin and FPN in breast cancer tissues and endocrine type, clinical characteristics and anemia.

Group	Hepcidin			FPN		
	Positive	Negative	χ^2 value	Positive	Negative	χ^2 value
Age	21	20	0.12	25	16	0.35
≤60	10	13		13	10	
>60						
Molecular typing	8	25	15.97**	25	8	7.58**
Luminal A+B	23	8		13	18	
HER2 Over-expression+Basal-like						
T staging	7	14	2.86	16	5	8.15**
T1	24	19		12	31	
T2, T3, T4						
Metastasis of lymph node	17	9	5.04*	11	15	5.29*
Yes	14	24		27	11	
No						
ER/PR	7	24	16.09**	24	7	8.12**
Positive	24	9		14	19	
Negative						

*P< 0.05, **P< 0.01, all P > 0.05, ER = estrogen receptor, PR = progesterone receptor, FPN = ferroportin

Table 2. Relationship between the expression of Hepcidin and FPN in breast cancer tissues and anemia

Group	FPN		Hepcidin	
	Positive	Negative	Positive	Negative
Anemia	9	5	7	7
Without anemia	29	21	26	24

FPN = ferroportin

cancer tissue and anemia ($\chi^2 = 0.18$, 0.02, respectively, all $p > 0.05$, Table 2).

Correlation between the expression of ferroportin and hepcidin

Twelve of 38 patients showed FPN expressed hepcidin, and 19 of 26 patients showed hepcidin expressed FPN ($\chi^2 = 10.64$, $p < 0.01$).

DISCUSSION

Studies have shown that iron may have a synergistic role in the process of tumor growth and differentiation; therefore, tumors have been shown to require increasing amounts of iron. The abnormal expression of proteins that regulate iron metabolism could significantly affect tumor proliferation and metastasis[16]. Brookes *et al*[17] showed that the down-regulation of FPN and the increase in iron in the cells of patients with intestinal cancer were related to tumor proliferation. At the same time, the increase in iron in cells could also lead to the down-regulation of E-cadherin, which would further increase the invasiveness and metastatic behavior of tumors. However, an increase in intracellular iron could promote the initiation and development of tumors by stimulating the Wnt signaling pathway[18]. In a recent study, Pinnix *et al* and Igor P [19,20] demonstrated low expression of FPN mRNA in patients with breast cancer, but high expression of hepcidin mRNA. Interestingly, the expression level of both the proteins was significantly related to the prognosis of patients with breast cancer. Our study confirmed that the expression of hepcidin and FPN in breast cancer tissue was associated with the molecular type, expression of ER/PR, and lymph node metastasis; also, FPN was related to the T stage, and neither FPN nor hepcidin was associated with anemia.

After detecting the expression of hepcidin and FPN in tissue from 64 patients with breast cancer by immunohistochemistry, we found that the positive expression rate of hepcidin was significantly higher in breast cancer than in normal tissue adjacent to the tumor ($p < 0.05$). Additionally, we determined and the positive expression of hepcidin was related to lymph node metastasis. Although the expression of FPN in tumor tissues and normal tissues was not significantly different ($p = 0.07$), the positive expression rate was clearly lower in breast cancer tissue than in normal tissue adjacent to the tumor, and the negative expression of FPN was associated with T stage and lymph node metastasis. The results showed a correlation between the expression of hepcidin and FPN in patients with breast cancer who had local invasion and lymph node metastasis.

In addition, Zhang S[21] *et al* found elevated concentration of plasma hepcidin in breast cancer patients, which is consistent with our findings. They also found that tumor hepcidin expression was marginally increased in breast tumors relative to adjacent tissues. In contrast, tumor ferroportin concentration was greatly reduced in breast tumors, compared to adjacent tissues. The author also found that reduction of hepatic hepcidin suppressed tumor growth, downregulation of tumor hepcidin suppressed tumor growth, which suggested that hepcidin – ferroportin might be a promoter for breast cancer growth. But the study did not detect the plasma levels of FPN, nor did it analyze the relationship between levels of hepcidin, FPN in plasma and tissues. Therefore, further research needs to be conducted to understand the relationship between levels of hepcidin, FPN in plasma and tissues, and their relationship with clinical features of breast cancer patients.

Breast cancer tumors are highly heterogeneous. Recently, the establishment of molecular typing of breast cancer based on differences in gene expression has provided important insights into the heterogeneity of tumors, rationale for staging, accuracy of the predicted prognosis, and personalized treatment. Therefore, we compared the immunohistochemical results for patient tissue samples with the endocrine type and found that the positive expression rate of hepcidin was lower in the group of patients with luminal A and luminal B types (good prognosis) than in the group of patients with the HER2 over-expression and basal-like types (poor prognosis) ($p < 0.01$). The expression of FPN was higher in the group with a good prognosis. Meanwhile, the expression of hepcidin was obviously higher in the ER-negative group than in the ER-positive group, while the positive expression rate of FPN was obviously higher in ER-positive patients than in ER-negative patients. The results showed that the expression of both hepcidin and FPN was significantly correlated with the molecular type, which could be used to predict the prognosis of breast cancer patients. Previous studies have demonstrated that the expression of hepcidin was correlated with FPN expression in breast cancer tissue, indicating that FPN was one of the downstream targets of hepcidin in breast cancer, and that hepcidin could regulate the metabolism of iron by inducing decreased expression of FPN and degradation of FPN[11,22].

Hepcidin is believed to play a key role in anemia in patients with chronic diseases including chronic inflammatory diseases and malignant tumors[23,24]. The increased expression of hepcidin could promote decreased expression and degradation of FPN, increase iron storage, reduce iron output, and eventually result in the loss of iron, leading to anemia[7,8]. Previous studies have demonstrated that high expression of hepcidin in serum from patients with tumors can cause anemia[1,8,9]. The same as the report of Ward *et al*[25] in colorectal cancer, our study showed that the expression levels of hepcidin and FPN in breast cancer tissue were not correlated with anemia too. Therefore, we presumed may be the local expression of hepcidin and FPN in tumor tissue was not related to the expression in serum. Further experiment should be needed to confirm the relationship among the local expression of hepcidin and FPN in tumor tissue, the expression in serum and anemia.

In summary, the expression of FPN and hepcidin in breast cancer tissue was related to clinicopathological characteristics such as the endocrine type, T stage, and ER/PR expression status. This index could be significant in terms of predicting patient prognosis and will guide personalized treatment.

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Conflict of interest: All authors have no conflict of interest regarding this paper.

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Original Article

Hypoxic Status and Radiotherapy Curative Effect of Nasopharyngeal Carcinoma Detected on 99mTc-HL91 Imaging

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ABSTRACT

Objectives: This study aimed to investigate the hypoxic status of nasopharyngeal carcinoma (NPC) before and after three-dimensional conformal radiotherapy (3-D CRT) and the correlation between hypoxic changes and radiotherapy curative effects.
Design: Retrospective study
Setting: Department of Nuclear Medicine, Sun Yat-sen University Cancer Center; Guangzhou, China
Subjects: Routine technetium-99m 4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione dioxime (99mTc-HL91) single photon emission tomography (SPECT) of the nasopharynx and neck was performed before and after 3-D CRT in 38 patients with NPC.
Interventions: An analysis of the target/non-target (T/N) value of the focus was performed.
Main outcome measure: T/N value of the nasopharyngeal focus and neck.
Results: The focus hypoxic examination of 32 of 38 patients was positive (84%). T/N values for hypoxic status in the 32 patients with a positive nasopharyngeal focus and normal tissue were 1.89 ± 0.95 and 1.18 ± 0.36, respectively. The mean T/N values for NPC hypoxic focus before and after radiotherapy were significantly different among the 32 patients. The hypoxic status of the nasopharyngeal focus positively correlated with its response to radiotherapy. The correlation coefficient was 0.641.
Conclusions: 99mTc-HL91 hypoxic imaging can reveal the hypoxic status of the NPC focus. The hypoxic status of NPC was closely correlated with the curative effect of 3-D CRT.

KEYWORDS: hypoxia, nasopharyngeal cancer, radionuclide imaging, radiotherapy

INTRODUCTION

Recent research studies discovered that hypoxic cells are present in almost all solid tumors[1]. Most hypoxic cells tend to not proliferate at all or proliferate slowly, so they are not sensitive to radiotherapy, which is an important reason why solid tumors are difficult to cure[2]. The oxygenation level and its changes in tumor tissue are important predictive indices of the efficacy of tumor radiotherapy[3]. Accurate measurement of the hypoxic status of tumors is important to detect pathological changes in tumor development that affect its clinical diagnosis and treatment[4]. Tumor hypoxic imaging, which can noninvasively detect the hypoxic area in tumor tissue, is applied to guide the treatment of and evaluate the prognosis of tumors[5].

Nasopharyngeal carcinoma (NPC) is an endemic disease within specific regions in the world[6] and is a highly malignant solid tumor. Despite NPC being a locoregionally advanced disease, a significant proportion of these patients respond well to radiotherapy[7]. Cervical lymph node metastasis is the main mode of dissemination[8], which always occurs early and is difficult to detect on magnetic resonance imaging (MRI) or computed tomography (CT). Thus,

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the range of radiotherapy needs to be identified, especially for the nasopharyngeal primary tumor and regional lymph nodes [9].

A research group reported that the rate of lymph node and contralateral level III/Val metastases was <1% in patients without contralateral retropharynx/ level II involvement[10]. The target volume coverage should be reduced in patients with lateralized primary NPC, which may assist in protecting the cervical organs at risk, including the thyroid, larynx, and esophagus[10]. Technetium-99m 4, 9-dinitrogen-3, 3, 10, 10-retramethyl dodecane-2, 11-dimethylglyoxime (99mTc-HL91) is a good imaging agent to identify hypoxic tissue. It has frequently been used in single-photon emission computed tomography (SPECT) hypoxic imaging research in recent years[11]. In this study, we used 99mTc-HL91 SPECT/CT hypoxic imaging to detect 99mTc-HL91 in the hypoxic tissue of the NPC focus and to determine its function as a guide in three-dimensional conformal radiotherapy (3-D CRT) in 38 NPC patients before and after 3-D CRT. In addition, we conducted preliminary research into the hypoxic status and changes in hypoxia in association with the radiotherapy curative effect.

MATERIALS AND METHODS

Research objective

The study subjects were 38 patients with NPC, who were treated and diagnosed at the Sun Yat-Sen University Cancer Center between June 2004 and April 2005. Among these patients, 30 were men and eight were women, and their age ranged from 24 to 74 years (median, 47.5 years). The World Health Organization pathological types were defined as follows: four cases of differentiated no keratinizing squamous cell carcinoma and 34 cases of undifferentiated no keratinizing squamous cell carcinoma. According to the clinical and MRI examinations (SIGNA CV/I 1.5T, GE Company, Milwaukee, US), the clinical stages of the tumors were as follows: T1 stage in one case, T2 stage in 10, T3 stage in 17, and T4 stage in 10. The Karnofsky Performance Status score in all patients was ≥90. No lesions were observed in the liver, kidneys, or heart. No obvious abnormal results were found on the blood and urine routine examinations. All of the patients underwent 3-D CRT. The study was conducted in accordance with the declaration of Helsinki. An approval from the Ethics Committee of Guangzhou First People's Hospital was also procured. Written informed consent was obtained from all participants.

Radiotherapy and efficacy evaluation

All 38 patients were treated with a conventional irradiation method (CT-SIM, Somatom Spirit, Siemens AG FWB: SIE, NYSE: SI, Munich, Germany). First, conventional external irradiation was performed at an absorbed dose of 40 Gy. Then, late-course 3-D CRT (Elekta Precise, Siemens AG FWB: SIE, NYSE: SI) was delivered to the NPC hypoxic target region until the absorbed dose reached 75 - 85 Gy.

Imaging methods and image analysis

99mTc-HL91 was provided by the Guangzhou Isotope Service Center of Chinese Atomic Energy Research Institute of Academy of Sciences. All labeling rates were greater than 95%. After the patients were injected intravenously with 99mTc-HL91 (total dose of 1110 MBq) over 1.5 h, esophageal SPECT was performed with the Millennium VG + Hawkey dual probes SPECT/CT system (GE Company, US) equipped with a low-energy high-resolution collimator. The dual probes were placed on the patients' neck and chest, rotating 360°. Data were collected through backstage attenuation correction to reconstruct images to the maximum expected value by the advance group, and then merged with the CT images by using the same machine to reconstruct the three-dimensional blending image. For image analysis, two nuclear medicine physicians blinded to clinical details evaluated the images for abnormal 99mTc-HL91 uptake. The focal radioactivity concentration area on the corresponding different axial SPECT images was defined as the focus of hypoxia, after excluding physiological uptake. Then, semiquantitative analysis was used to calculate the focus target/non-target specific value (T/N). The strongest focus uptake on the cross section or coronal plane of the radioactivity image was used to calculate T/N.

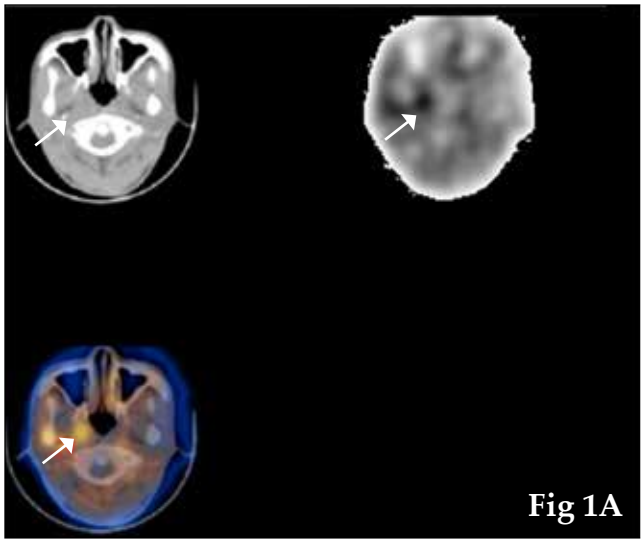
Statistical analysis

SPSS 10.0 software was used. The T/N values of the hypoxic status with nasopharyngeal focus and normal nasopharyngeal tissue were compared by using a paired *t*-test, as well as the mean T/N before and after radiotherapy. The hypoxic status of the nasopharyngeal focus and its response to radiotherapy were evaluated by using the Pearson correlation analysis test.

RESULTS

Imaging of nasopharyngeal tumors with 99mTc-HL91 injection

The patients were injected with 99mTc-HL91 without any discomfort. The 99mTc-HL91 was selectively concentrated in the nasopharyngeal tumor tissue, which was clearly observed on imaging. In the 38 NPC patients, 99mTc-HL91 hypoxic imaging was performed 38 times, before and after radiotherapy. Of the NPC patients, 32 had positive hypoxic imaging results, with a hypoxic examination positivity rate for an NPC focus of 84%.



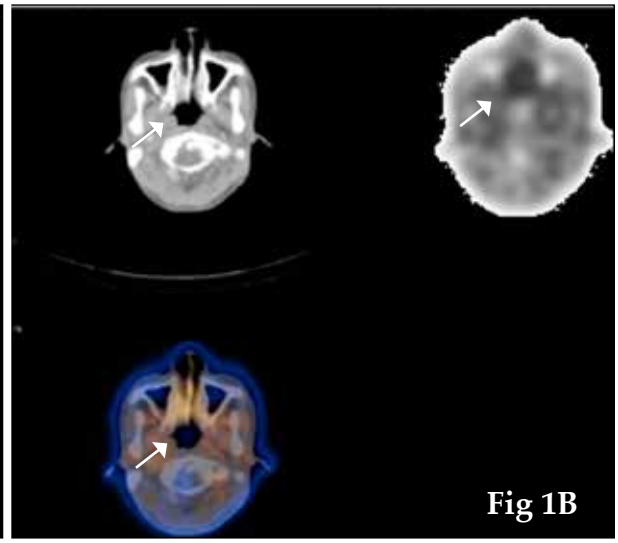


Fig 1; Case 1: Male, 51 years old, undifferentiated nasopharyngeal non-cancroid
A: The hypoxia imaging of nasopharyneal focus SPECT/CT fusion image at the same machine was positive before radiotherapy, T/N value was 2.11 (arrow).
B: The hypoxia imaging of nasopharyneal focus after the hypoxic focus was treated by 3DCRT was weakly positive, T/N value was 1.23 (arrow).

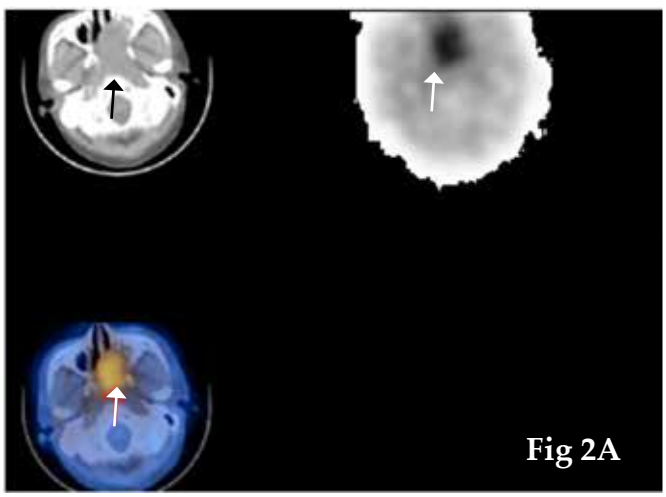
Therapeutic effect of 3-D CRT detected on tissue radioactivity imaging

The count ratio of the nasopharyngeal focus showing radioactivity concentration to that of normal nasopharyngeal tissue radioactivity was 1.89 ± 0.95 in the 32 patients with positive hypoxia imaging. Their count ratio of the nasopharyngeal focus showing radioactivity non-concentration to that of normal nasopharyngeal tissue radioactivity was 1.06 ± 0.18. Using the paired *t*-test, the differences were significant ($p < 0.001$).

The T/N values of the NPC hypoxic focus of the 32 NPC patients before and after 3-D CRT were 1.89 ± 0.95 and 1.18 ± 0.36. After comparison, the *t* value was 4.993, and the difference was significant ($p < 0.001$). The hypoxic status of the nasopharyngeal focus was positively correlated with its response to 3-D CRT. The correlation coefficient was 0.641 ($p < 0.01$).

The therapeutic effect of 3-D CRT based on prognosis

The short-term effect of 3-D CRT in the 38 NPC patients was significant. The local tumor control rate was 94.6%, the prevalence rate of acute radiation injury was 78.0%, dry mouth was observed in 65.3% of the patients, and the patients' quality of life improved.



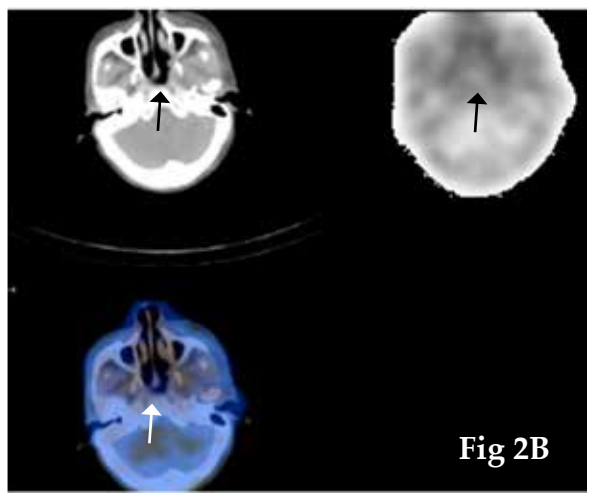


Fig 2; Case 2: Male, 42 years old, undifferentiated nasopharyngeal non-cancroid
A: CT scan indicated that nasopharyneal focus invaded nasal cavity; before radiotherapy, the hypoxic imaging of nasopharyneal focus was strongly positive, T/N value was 4.83 (arrow).
B: The hypoxia imaging of nasopharyneal focus after the hypoxic focus was treated by conformal therapy was weakly positive, T/N value was 1.27 (arrow). It indicated that nasopharyneal carcinoma focus was improved after 3DCRT.

Case 1 was an undifferentiated nasopharyngeal non-cancroids without invasion (Fig 1), and case 2 was an undifferentiated nasopharyngeal non-cancroids with invasion of the nasal cavity (Fig 2). The assessment results before (A) and after (B) 3-D CRT indicated that the condition of both of these patients with NPC improved after treatment with 3-D CRT.

DISCUSSION

NPC is also called "Guangdong tumor." Worldwide, 80% of NPC cases occur in the south of China[12]. At present, radiotherapy is the preferred treatment method, but the 5-year survival rate of NPC patients has remained between 50% and 60%[13]. Therefore, developing a method that can enhance and monitor the treatment effect on NPC is the focus of the present study. Detecting the hypoxic level of the cancer focus before and after cancer treatment can evaluate the curative effect and contribute to developing a therapeutic schedule, during which radio-resistance might develop[14].

Many factors affect radiotherapy and local tumor control. The role of the tumor oxygenation status has been a recent subject of attention. Both tumor regression and the local control rate of tumor response to radiotherapy are significantly affected by the hypoxic level[15]. Hypoxic imaging uses radio-labeled hypoxic imaging agents that penetrate tumor tissue. The imaging agent is retained because of the hypoxia, and visualizing the hypoxic agent on SPECT or PECT reveals the tumor's dynamic hypoxic state[16].

99mTc-HL91 is a by-product of the nitroimidazole group. Its synthesis is simple, it is easy to label, its labeling rate is high, without cytotoxicity, it can be safely used, and it is stable. Because it is a 99mTc-labeled compound, it is suitable for SPECT imaging. Determining the nature of and quantitatively determining the hypoxic focus can dynamically detect tumor hypoxia and predict the efficacy of radiotherapy. Therefore, this agent has many advantages over other hypoxia detecting techniques[17].

The current study found that 99mTc-HL91 mainly concentrated in the hypoxic focus of NPC. It could clearly locate the NPC focus, and hypoxic imaging could clearly reveal the hypoxic state of the NPC focus, consistent with the findings of previous reports. The 99mTc-HL91 uptake rate was negatively related to blood perfusion. It was mainly concentrated in the hypoxic tissue of the focus, rather than the abundant blood or necrotic area[18].

99mTc-HL91 obviously concentrates in the hypoxic tissue of lung cancer. The degree of cancer focus differs, as well as its malignancy grade. A higher hypoxic state is associated with a poorer curative effect[19]. 99mTc-HL91 hypoxic imaging revealed the absence of an NPC bone metastasis focus[20], which might be related to the abundant blood supply and nonexistence of hypoxic cells in bone metastases. This also might be due to the few cases available. In six NPC cases, hypoxic imaging results were negative, perhaps due to the abundant blood supply and too few hypoxic cells in the nasopharyngeal focus.

Nordsmark and Overgaard[21] investigated the relationship between the oxygen partial pressure and local control rate in 35 patients with head and neck squamous cell carcinoma (the hypoxic group) during the progressive stage of the initial radiotherapy by using the oxygen electrode method to measure the oxygen partial pressure (2.5 mm Hg) and compared their results with the non-hypoxic group. Their results showed that the local control rate tumors that were well oxygenated before treatment reached 90%. However, in the hypoxic group, the control rate was just 45%. Dehdashti *et al* [22] performed ^{60}Cu-ATSM PET hypoxic imaging in 14 patients with cervical cancer. After evaluating the relationship between hypoxic degree and prognosis, they found that five patients whose tumor/blood (T/B) was >3.5 at 14 - 24 months of follow-up had local recurrence, but six of nine patients whose T/B was <3.5 had tumor-free survival. The analysis of overall survival rate also showed that the survival rate of the patients with T/B <3.5 was obviously higher than that of the patients with T/B >3.5. Vijayakumar *et al* [23] used 3-D CRT for malignant tumors and showed that it could observably enhance the target area volume dose and improve the coverage of the target area volume dose, making the tumors shrink quickly and eventually disappear without serious radiotherapy reactions. This study also showed that 99mTc-HL91 hypoxic imaging could clearly reveal the hypoxic state in the NPC focus.

In clinical settings, the radiotherapist can adjust the radiotherapy dose according to the hypoxic status of the nasopharyngeal focus during late-course radiotherapy and administer the NPC radiotherapy based on the structure of the hypoxic target area. Our results showed that the nasopharyngeal focus had clearly improved after radiotherapy. Its short-term effect was significant, the local tumor control rate was high, acute radiation toxicity was low, and the patients' quality of life improved.

The oxygen status of a cancer focus is closely related to its radio sensitivity. The number of tumor hypoxic cells increases a tumor's resistance to radiotherapy. Kinuya *et al* [24] reported that hypoxic imaging could detect the oxygen status of tumor cells during X-ray irradiation. At the same time, it could monitor the response of tumor hypoxic cells to radiotherapy. In an *in vitro* study, Suzuki *et al* [25] found that the hypoxic

status of tumor cells was closely related to their response to radiotherapy. They also found that the uptake of 99mTc-HL91 in tumor tissue was not always related to radio sensitivity. An increase of uptake in tumor tissue after irradiation indicated that the curative effect of radiotherapy was poor. However, a decrease or little change in the uptake by tumor tissue during radiotherapy indicates that radiotherapy might be effective. Further research showed that 99mTc-HL91 hypoxic imaging could monitor the hypoxic status and radiation reactions of NPC foci. Their nasopharyngeal hypoxic focus was closely related to the response to radiotherapy, which is consistent with our previous report[26].

The current study is a preliminary research into the relationship between hypoxic status and radiotherapy curative effect through 99mTc-HL91 hypoxic imaging used for observing changes in the oxygenation status during radiotherapy. In the future, we will conduct further research on tissue samples to study the relationship between hypoxic status and the radiotherapy curative effect on NPC from various perspectives.

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Case Report

A Case of Scrub Typhus Encephalopathy

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ABSTRACT

Scrub typhus, caused by *Orientia tsutsugamushi*, is prevalent in the tropical areas like South-East and Far East Asia. A seven-year-old Indian boy who had recently returned from India, presented with fever, headache, vomiting and convulsions refractory to anticonvulsants and multiple antimicrobials. He was diagnosed as a case of Scrub Typhus by Weil-Felix test. He responded well to a ten day course of chloramphenicol. A huge population in Kuwait travels to and from the areas endemic for Scrub typhus. A clinical suspicion is prudent in all such cases presenting with a pyrexia of unknown origin. In cases with involvement of the central nervous system, chloramphenicol should be the first choice of treatment, as it penetrates the blood brain barrier well.

KEY WORDS: *orientia tsutsugamushi,* pyrexia, typhus fever

INTRODUCTION

Scrub typhus, caused by *Orientia tsutsugamushi* (an alpha proteobacterium belonging to the family Rickettsiaceae), is prevalent in the south-east Asia, Far East and Australasia (the 'Tsutsugamushi triangle')[1]. It is transmitted through the bite of the infected chiggers (larvae) of trombiculid mite (*Leptotrombidium deliensis* in India and *L. akamushi* in Japan)[2]. Mortality is 15%, mostly due to missed or delayed diagnosis[3]. It is a re-emerging infection in many countries due to increased usage of betalactam antibiotics and increasing urbanisation in the rural areas[4].

In India, after the outbreaks in the subhimalayan and southern regions, scrub typhus is now a re-emerging infection[5, 6]. After a resurgence among armed troupes in 1990[7], the organism has shown its endemic presence in the northern as well as the southern parts of India[8-10]. Owing to the nonspecific symptoms, its clinical diagnosis is difficult. Moreover, anti rickettsial drugs are not part of any empirical therapy for a fever of unknown origin. Kuwait harbours a huge immigrant population hailing from the Indian subcontinent. Hence suspicion, diagnosis and treatment of this infection in the travellers coming from these areas become important.

After a careful search of the literature, no publication regarding a scrub typhus case could be found from Kuwait. The aim to report this case is to increase the awareness about clinical suspicion, diagnosis and management of such an infection.

CASE REPORT

A previously healthy 7-year-old Indian boy who had returned from India two days back, presented to the Paediatric Casualty with four days' history of fever, headache and vomiting. In the Casualty the patient developed a brief episode of generalised tonic-clonic convulsions, so he was admitted for further management. Later in the day, the convulsions became recurrent, associated with urinary incontinence and drowsiness. With a suspicion of meningoencephalitis, cefotaxime and acyclovir were started in antimeningitic dosages along with multiple anticonvulsant agents. The blood counts, renal and hepatic function tests were all within normal limits. CT scan of brain (done on admission then after 48 hours), magnetic resonance

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arterio- and venography, and cerebrospinal fluid (CSF) study were unremarkable on admission. Due to a deterioration in the level of consciousness and continued convulsions, he was intubated and kept on mechanical ventilation in the Paediatric Intensive Care Unit (PICU) .

After completing 10 days on cefotaxime and acyclovir, the child still had spikes of temperature (up to 39.5 °C). Haematological tests revealed WBC 6.8 x 10^9/L, neutrophils 52 x 10^9/L, lymphocytes 30 x 10^9/L, haemoglobin 12 g/L, RBC 4.18 x 10^{12}/L, platelets 440 x 10^9/L and erythrocyte sedimentation rate 51 mm in the first hour. Blood biochemistry showed serum sodium 139 mmol/L, potassium 4.7 mmol/L, calcium 2.13 mmol/L, chloride 99 mmol/L, urea 5.4 mmol/L, creatinine 41 μmol/L and C-Reactive Protein 61.1 mg/L. Repeated CSF study was unremarkable, without showing any growth on culture. All specimens of blood and urine, repeated for culture twice a week during the child's stay in PICU, did not show any growth.

In the PICU, cefotaxime was replaced with meropenem 400 mg IV q8h. Intravenous immunoglobulin and prednisolone were added to the treatment.

A plethora of laboratory tests were done, eventually all came out to be negative. These included *Clostridium difficile* toxin in stool, peripheral blood film examination for malaria (three times), immunochromatographic antigen-detection test for *Plasmodium vivax* and *P. falciparum*, T-spot test for latent tuberculosis, antibody agglutination test for *Brucella* spp., Widal test, cryptococcal antigen in blood and CSF, *Leptospira* IgG & IgM, humoral and cell mediated immune responses, HIV antibodies, hepatitis C virus antibodies, hepatitis B virus surface antigen, Polymerase Chain Reaction (PCR) for herpes simplex virus, parvovirus, Japanese encephalitis virus, cytomegalovirus, enterovirus, Epstein-Barr virus, *Rickettsia* spp. (typhus group), and *Rickettsia rickettsiae*.

On day 14, the patient was still febrile, ventilator-dependent and was having convulsions. Acyclovir was stopped and teicoplanin 200 mg IV q12h was started empirically. The Weil-Felix test was performed with Febrile Antigen Test kit (PLASMATEC, UK) using OX 19, OX 2 (both from *Proteus vulgaris*), and OX K (from *P. mirabilis*) antigens. After 24 hours' incubation, the test showed a positive agglutination in the tubes with OX K, up to 1:80 dilution, and negative in all the dilutions for OX 19 and OX 2 antigens. On re-examining the patient's skin, no rash or sign of eschar was found, nor there was any past history of such a lesion provided by the parents. Post contrast CT scan brain was repeated, but was unremarkable. A presumptive diagnosis of Scrub Typhus was made and intravenous clarithromycin 150 mg IV q12h was started on day 15. After two days clarithromycin was replaced by azithromycin 200 mg q24h through nasogastric tube. Although some studies recommended Clarithromycin[5], this change was made in line with many other studies recommending Azithromycin as a better choice[3, 11]. But 48 hours later, the patient continued to have fever (39.2 °C), leukocytosis (26.7 x 10^9/dl) and convulsions. His electroencephalogram (EEG) was suggestive of epileptic encephalopathy. Intravenous chloramphenicol 450 mg IV q6h was added to the treatment.

Within four days, the patient became afebrile, WBC count came down to 6 x 10^9/dl and convulsions stopped altogether. Meropenem was stopped after completion of 10 days, and teicoplanin after two weeks. The patient was extubated and shifted to the general ward. Chloramphenicol was given for a total of 10 days. The blood counts were kept under a close watch during and after the course of chloramphenicol, in order to control bone marrow suppression due to chloramphenicol, if any. On the last day of chloramphenicol treatment, the counts were back to the pre-chloramphenicol base line of WBC 5.5 x 10^9/L, neutrophils 3.4 x 10^9/L, lymphocytes 1.3 x 10^9/L, RBC 4.3 x 10^{12}/L, haemoglobin 121 g/L, platelets 217 x 10^9/L. After 24 hours of stopping chloramphenicol, blood counts showed WBC 5.9 x 10^9/L, neutrophils 4.1 x 10^9/L, lymphocytes 0.97 x 10^9/L, RBC 5 x 10^{12}/L, haemoglobin 138 g/L and platelets 205 x 10^9/L. There was no bone marrow suppression due to chloramphenicol. MRI brain with contrast done on 23rd day of admission reported the changes suggestive of encephalopathy of hypoxic or infective origin. On 24th day the OX K was still in the titre of 1:80, but became completely negative on repeating the test on 42nd day (two weeks after completing the treatment). Unfortunately, by that time the child had developed generalised spastic rigidity due to the prolonged hypoxic insult to the brain. So he was prescribed physiotherapy.

DISCUSSION

The presented case was diagnosed as a probable case of Scrub Typhus encephalopathy based upon the clinical and serological findings. Encephalopathy constitutes 15% of all scrub typhus cases. Other complications include meningitis, meningoencephalitis, encephalitis, renal failure, myocarditis, gastrointestinal hemorrhage, gangrene, disseminated intravascular coagulation, shock, acute pneumonia, respiratory distress syndromes and haemophagocytic syndrome[5]. The possibility of a serological cross-reaction due to rickettsiae other than *O. tsutsugamushi* was excluded by serological tests (Enzyme-Linked Immuno-Sorbent Assay) for other rickettsiae, as a specific Polymerase Chain Reaction

(PCR) test for *O. tsutsugamushi* was not available in Kuwait. Enzyme-linked assays for *Rickettsia typhi*, *R. prowazekii* and *R. rickettsii* IgG and IgM were negative, while the same for *O. tsutsugamushi* were not available.

As in our case, the characteristic eschar is absent in 40% of the cases, especially in the south-east Asian population[2, 4].

The diagnostic cut-off for scrub typhus in the Weil-Felix test has been a point of much debate. Although it is globally agreed that a four-fold rise in OX K antibodies in a Weil-Felix reaction is diagnostic, various workers have used the cut-off in a single serological test ranging from 1:10 to 1:400[12] . It varies in the different populations of the world, depending upon the endemicity. In a recent study from India, the cut-off has been shown to be 1:80[13]. Most of the outbreak reports depend upon the clinical findings and antibody titre of 1:80 or over in Weil-Felix reaction[14]. Being a heterophile agglutination reaction, the test has a low sensitivity, yet a reasonably high specificity[15]. Our case had a constant titre of 1:80 on the first two occasions tested 10 days apart. This test detects IgM antibodies. The delayed suspicion of the condition leading to a delayed test (14th day of admission) may well explain the agglutination titre as low as the cut-off. On repeating 18 days after completion of the ten day course of chloramphenicol, the test was negative in all dilutions. In addition, the patient showed marked clinical improvement.

There are other non-culture diagnostic tests for Scrub Typhus. They all have their own pitfalls as well as advantages. The Indirect Immunofluorescence Antibody (IFA) test suffers from the high antigenic variability in *O. tsutsugamushi* . Culture requires time and expertise, and has a low sensitivity. Polymerase chain reaction also has its problems like a high antigenic variability among different strains of *O. tsutsugamushi*, and a significantly less sensitivity on blood samples as compared to on the eschar tissue. This is an issue for the patients who do not develop an eschar[16]. Loop Isothermal Amplification has been reported as an inexpensive yet highly sensitive and specific molecular technique for diagnosis of Scrub Typhus[17].

A specific, sensitive and low-priced test is warranted for this infection which is prevalent in the southern and south-eastern Asia, from where the population is always moving to the more developed countries. In a multicentre survey, scrub typhus was diagnosed in 5.7% of the international travellers, majority of whom acquired it in South-Central or South-East Asia[18]. In areas like Kuwait, where *O. tsutsugamushi* transmission is virtually nonexistent and diagnosis among the travellers is a challenge, clinical suspicion is the key.

CONCLUSION

This case is being reported here to highlight the importance of clinical suspicion of the infection and to include scrub typhus as a differential diagnosis for the travellers with pyrexia coming from endemic areas. This is also imperative to underline the need to develop a reliable and confirmatory molecular or fluorescent antibody diagnostic test in Kuwait. Any delay in diagnosis might be a cause of grave consequence for the patient.

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Case Report

Urinary Bladder Fistula due to a Complicated Ovarian Dermoid Cyst

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ABSTRACT

Ovarian dermoid cysts (mature cystic teratomas) are a benign type of germ cell tumours and the most common ovarian neoplasms in women of fertile age. We demonstrate a rare case of ovarian dermoid cyst complicated with a urinary bladder fistula presenting with irritative lower urinary tract symptoms which managed successfully with laparoscopic approach.

KEYWORDS: laparoscopy, mature cystic teratoma, ovarian dermoid cyst

INTRODUCTION

Dermoid cysts are the most common germ cell tumours. The tumor arises from multipotent cells of the ovary and develop into ectodermal, mesodermal and endodermal structures[1]. The peak incidence of dermoid tumors is between 20 and 40 years of age. It can be bilateral in up to 15% of cases[2]. They are often asymptomatic, most of them discovered incidentally during pelvic ultrasound scan or during pelvic inspection during laparoscopy or laparotomy[3].

CASE REPORT

A 29-year-old unmarried Asian female, non smoker, with no previously significant medical and/or surgical history presented with recurrent attacks of right iliac fossa pain and dysuria for one month, Irregular menses with no change in bowel habits. Clinically she was afebrile with tender right iliac fossa. Her laboratory investigations revealed normal CBC and renal function tests, many WBCs on urine analysis but no growth on urine culture and negative pregnancy test. Abdomino-pelvic U\S and CT with contrast revealed well defined right adnexal cyst 3.8 x 3.7 cm showing mural and septal enhancement and harboring fat and fluid content, coarse calcifications well as multiple air foci suggesting infected terato-dermoid cyst (Fig 1). This cyst is closely related to right lateral wall of urinary bladder with suspected small fistulous communication to urinary bladder. Urinary bladder is diffusely thickened with minimally enhancing wall and perivesical fat stranding impressive of cystitis. Tumor markers (CA125, CA 19-9, CEA, SCCA) were in normal range. Patient was treated initially by injection antibiotics Peroperative prophylactic injection of antibiotics (Cefotaxime 1g x 3) was initiated then the cystoscopy examination revealed a polypoidal growth(fistula) at the dome of the bladder covered with a whitish deposit (Fig 2). Fistulogram showed a 2 cm fistula-tract between the urinary bladder and the right ovary. Diagnostic laparoscopy showed the right ovary was connected to the the dome of the bladder with a stalk (Fig 3). The urinar bladder fistula , along with the stalk and the right ovary, was excised in toto (excision of the dermoid cyst along with partial cystectomy) (Fig 4). Histopathological examination showed numerous hair follicles surrounded by fibrofatty tissue containing mature adipocytes along with the presence of skin adnexal structures. The postoperative period was uneventful,10 days later the cystogram showed intact urinary bladder wall without any leakage of contrast. After removal of

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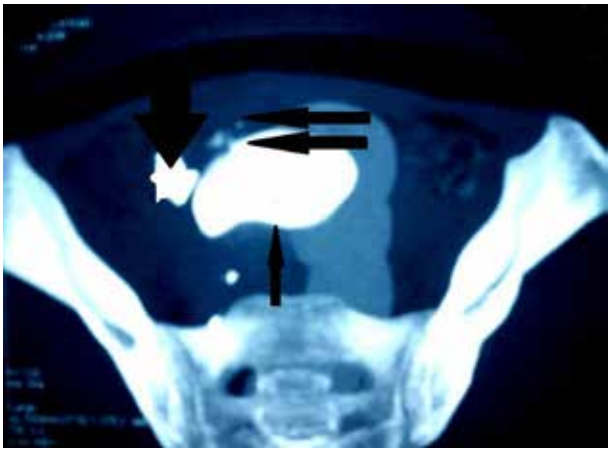

Fig.1: CT(abdomen, pelvis): arrow upward : urinary bladder, Thick arrow : right ovary, double arrow : fistula- tract.

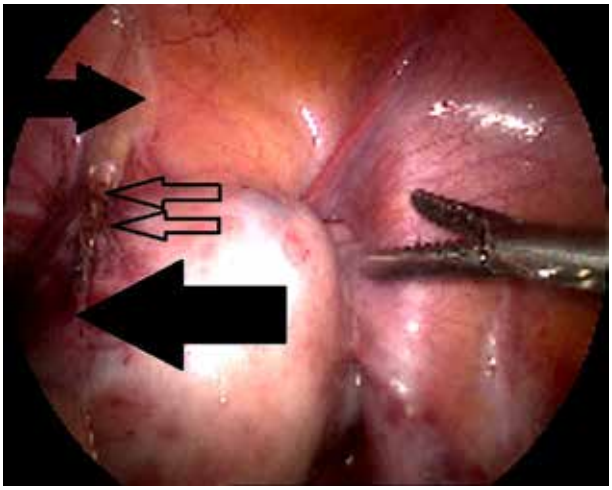

Fig. 3: a) Laparoscopic view: toparrow : urinary bladder, thick arrow : right ovary, double arrow : fistula-tract.

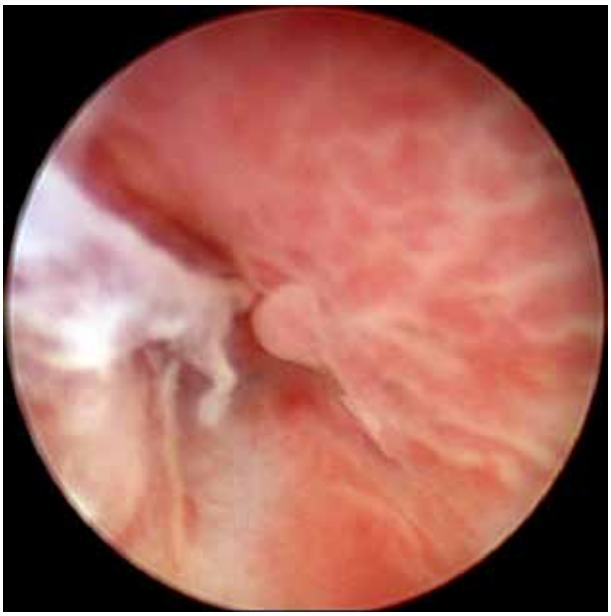

Fig. 2: Cystoscopic view of the urinaray bladder fistula

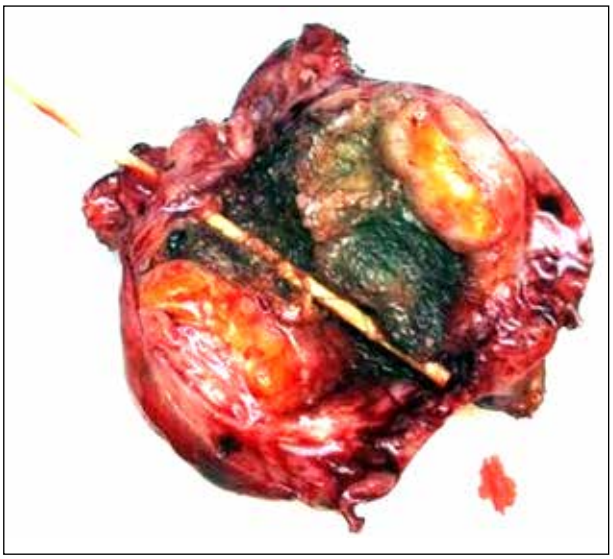

Fig. 4: Photograph shows the excised right dermoid ovarian cyst communicated with a urinary bladder fistula

the Foley catheter, the patient voided with a good stream. Follow up annually for five years: clinically, ultrasound (abdomen, pelvis), urine-culture showed no recurrence of urinary tract infections or urinary bladder fistula.

DISCUSSION

Our patient's complications included torsion, rupture into the peritoneum, malignant transformation (1 - 2%), infection (1%), and invasion into the adjacent viscera which is least common[4]. The bladder is the most common site of spontaneous perforation[5]. Presenting complaints are irritative lower urinary tract symptoms, pyuria, the passage of seborrhoeic gravels, and the passage of hairs (pilimiction). The passage of hairs is a pathognomonic sign[6].

Chronic leakage of the seborrhoeic material leading to inflammation and also compression on the bladder wall leading to ischemic focal wall necrosis and exposure to contents appears to be the cause of invasion and fistulization into the bladder[7].

Squamous cell carcinoma is the most common type of malignant transformation in mature cystic teratoma[8]. The risk factors for malignant degeneration are: old age, large tumours, increased growth rate and high levels of tumor markers (CA125, CA 19-9, CEA, SCCA)[9,10].

An abdominal plain X-Ray may show calcified density images compatible with the teeth, suggesting the possibility of a benign teratoma[11]. Most of them can be diagnosed by transabdominal ultrasonography (US), transvaginal US, computed tomography (CT) or

magnetic resonance imaging (MRI)[12]. Characteristic findings on CT include a fat-containing mass, which contains a mixture of fat, hair, debris, and fluid. With diagnostic significance are calcifications, including teeth and bone[13].

The classic treatment for benign ovarian dermoid included cystectomy and oophorectomy using an open approach which is preferred for large or bilateral teratomas and in cases where malignant degeneration is suspected[14]. Gradually, laparoscopic cystectomy, using closed technique to avoid spillage of the cyst contents into the abdominal cavity, took over due to lower complications rate with similar rates of safety and efficacy with advantages include improved magnification, less intraoperative blood loss, less postoperative pain, shorter hospital stay, lower postoperative morbidity, shorter recovery time and not least better cosmetic result[15]. In the situation of suspicious lesions they should be biopsied for frozen section and free fluid in the peritoneal cavity should be sent for cytological examination.

CONCLUSION

Most of dermoid cysts are benign, but we have to follow a strict policy of preoperative evaluation and use of frozen section in complex cysts for diagnosis of early malignant transformation. However, clinical trials with a large number of patients are necessary to compare the surgical methods of management, But it can be efficiently treated *via* endoscopic surgery using closed technique to avoid spillage of the cyst contents into the abdominal cavity.

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Case Report

Scleral Buckling Surgery for the Repair of Binocular Combined Retinoschisis and Retinal Detachment: A Case Report

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ABSTRACT

Congenital retinoschisis is an uncommon ocular disorder, and combined retinoschisis and retinal detachment is rarer. Here, we report a case of binocular combined retinoschisis and retinal detachment in a 34-year-old male. We reattached the detached retina through scleral buckling. No recurrence of retinal detachment was found in each follow-up visit until the present. The satisfactory results of scleral buckling surgery for the repair of combined retinoschisis and retinal detachment indicate that this kind of patients can have the same surgery as those with ordinary rhegmatogenous retinal detachment.

KEYWORDS: congenital retinoschisis, ocular disorder, sclera, vitreoretinal dystrophy

INTRODUCTION

Congenital retinoschisis is a vitreoretinal dystrophy disorder that is characterized by cystoids degeneration of the stratum neuroepitheliale retinae and splitting of the nerve fibers layer. This disease can involve the posterior pole of the eye ground and periphery section. Vitreous hemorrhage and retinal detachment are the most severe complications of retinoschisis, which can usually lead to vision loss.

Combined congenital retinoschisis and retinal detachment is less common in the clinic. It is controversial whether sclera cingule surgery or vitreous surgery is the first choice[1,2]. Here, we report a case who suffered combined retinoschisis and binocular retinal detachment. We performed sclera extra-cushion and crush operation and obtained good results from the operation.

CASE REPORT

A 34-year-old male complained of blurred vision for 15 days in the left eye. He had presented with comparatively weak binocular vision when he was young without diagnosis and treatment. His best-corrected visual acuity (BCVA) was 0.4 in the right eye and 0.1 in the left eye. A fundus examination revealed split gossamer-like changes in the binocular periphery of the retina located in the bottom and grey-white retinal raise in the left eye, and other segments of binocular were normal. A diagnosis of binocular retinoschisis combined with retinal detachment in the left eye was therefore, made.

After careful examination, we found that there was outside layer hiatus inner retinoschisis located at the 5 o'clock position after tapping and with congealed vertex heading and pressing. We performed congealed and fixed compression with a 7 mm wide and 15 mm long sponge mat located outside of the corresponding sclera. On day-1 after surgery, the retina had completely returned to normal. During follow-up visits, no retinal detachment and recurrence of the left eye were found.

Several months later, the patient complained of decreased vision in the right eye. The results of ocular examinations showed that BCVAs of the right eye and the left eye were 0.1 and 0.15, respectively. There was local detachment at the infratemporal retina periphery in the right eye. The diagnosis upon

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admission was RRD in the right eye and binocular retinoschisis. The hiatus was not found in the right eye after examination by a three-mirror contact lens and an indirect ophthalmoscope before surgery. Therefore, we performed sclera extra-pad and press surgery in the right eye under local anesthesia. On day-1 after surgery, the retinal split was completely returned to normal. The follow-up examinations revealed that no retinal detachment and recurrence of the right eye was found.

DISCUSSION

Congenital retinoschisis is also called hereditary retinoschisis, which exists at birth, and is less common than acquired retinoschisis. Males are more prone to suffer congenital retinoschisis. The characteristics of congenital retinoschisis include a detached nerve fiber layer of the bottom retina and a yarn-like membrane that swells up and reaches the periphery. The blood vessel above the yarn membrane connects with the retinal blood vessel. This disease is mostly bilateral and prone to nystagmus, which usually affects the inferior temporal quadrant. Once split into two layers with the hiatus, retinal detachment will occur.

With respect to therapy, retinoschisis patients who do not have retinal detachment or an endangered macular area will only be observed, and no surgical procedures will be performed. If the macular region is endangered, we will perform laser therapy surrounding the trailing edge of the split and perform dyke-like laser photo-coagulation at the juncture between the retinoschisis and the normal retina. The purpose of laser photo-coagulation is to form a scar conglutination and restrain the development of a split[3]. Also, some experts have pointed out that photo-coagulation might increase the risk of retinal detachment. As a result, it is still controversial whether laser therapy should be performed on patients with an involved macular region. For combined retinoschisis and retinal detachment patients, surgical therapies should be performed, including traditional extra-way surgery and vitreous body resection operation. Extra-way surgery is simple and impairment is small, which could prevent cutting the vitreous body. The subject range mainly includes patients who do not have proliferative vitreoretinopathy and patients whose split schizocele exinous hiatus is located in the anterior of the ambitus. For patients with split schizocele hemorrhage, vitreous hemorrhage, a split involving the macular area, or obvious vitreous body proliferation and drag, an operation on the vitreous should be performed[3]. For cases with tractional retinal detachment and repeated vitreous hemorrhage, vitreous surgery should also be the first choice. If necessary, air-liquid exchange and silicone oil filling should be performed. Particular attention should be paid to patients who suffer from congenital retinoschisis, including mostly children and young people. Proliferative vitreo-retinopathy easily occurs after operation on the vitreous and results in long-lasting complications, such as retinal detachment and relapse.

In this case report, this patient suffered successive binocular retinal detachment, but the detachment was located on the bottom and periphery of the retina and the scope was comparatively limited. Since the retinal detachment did not involve the macula and the hiatus was comparatively located in the periphery, we chose traditional extra-sclera pressing surgery to seal the detachment. The binoculars were followed up for three years, and retinal detachment and relapse did not appear constantly, which proved that for patients who suffer from congenital retinoschisis combined with retinal detachment, the key to successful surgery was to find and seal the outer hiatus. As long as reasonable surgery modes are chosen and carefully carried out, satisfactory treatment outcomes can be obtained.

CONCLUSION

The satisfactory results of scleral buckling surgery for the repair of combined retinoschisis and retinal detachment indicate that this kind of patients can have the same surgery as those with ordinary rhegmatogenous retinal detachment.

ACKNOWLEDGMENTS

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Conflicts of interest: None

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Case Report

An Extremely Rare Cause of Hematuria: Adamantinoma like Neuroectodermal Tumor of Bladder

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ABSTRACT

Primary primitive neuroectodermal tumour (PNET) is a rare entity and have severe malign potential. However, PNET is derived from central nervous system, it can rarely occur in another soft tissue. Herein, we present an extremely rare cause of hematuria in an 83-year-old man, who was diagnosed as adamantinoma like PNET, in bladder. After transurethral surgical treatment, there was no recurrence, in short-term clinical follow-up. According to our best knowledge, he was the oldest patient who had PNET in bladder, in published literature.

KEY WORDS: bladder tumor, malign tumors, urinary bladder neoplasms

INTRODUCTION

Primary primitive neuroectodermal tumor (PNET) is described in extraosseous soft tissue[1]. PNET belongs to the Ewing family of tumors which usually affects the bones. Additionally, it has a potential for affecting other soft tissues[2,3]. Nevertheless, PNET is an extremely rare type of tumor in bladder[4]. PNET is originated from neuroectodermal cells and are described as small rounded blue cells that exhibit a variable degree of neural differentiations, under microscope. PNET usually occurs in young adults and is rare in elderly. To our best knowledge, only 11 cases of PNET in bladder were reported, and here we present the oldest patient with adamantinoma like PNET in the bladder, in published literature[1].

CASE REPORT

An 83-year-old man admitted urology outpatient clinic with chief symptoms of increasing intermittent macroscopic hematuria and dysuria for four days. In detailed history, he had hypertensive heart disease and previous coronary by-pass surgery eight years ago. He was a smoker who gave up smoking, 10 years ago. He was using antihypertensive and anti-coagulant drugs including clopidogrel 75 mg and acetylsalicylic acid (ASA) 300 mg, once a day. Detailed physical examinations were normal. Urine analyses showed macroscopic hematuria and ultrasonography reported a solid mass which has 3 cm diameter at the doom of the bladder. There was no finding of stone, tumor and/or obstruction in upper urinary tract. Additionally, laboratory analyses including prostate specific antigen and haemoglobin levels were normal, but we found that international normalized ratio (INR) was increased to 2.4. Cystoscopy and transurethral bladder tumor resections (TURBT) were planned and computed tomography (CT) was performed for advanced preoperative evaluation (Fig 1a). There was no pathologic lymph node in pelvis and abdomen, in CT, and chest X-ray was normal. There was only slight thickening in bladder mucosa at the dome of bladder in CT slides.

Clapitogrel and ASA were stopped and low molecule weight heparin was administered by parenteral route. When INR was at level of 1.5, cystoscopy was performed. There was a bleeding, sessile globular, and solid looking tumor which was originating from the dome of bladder, in

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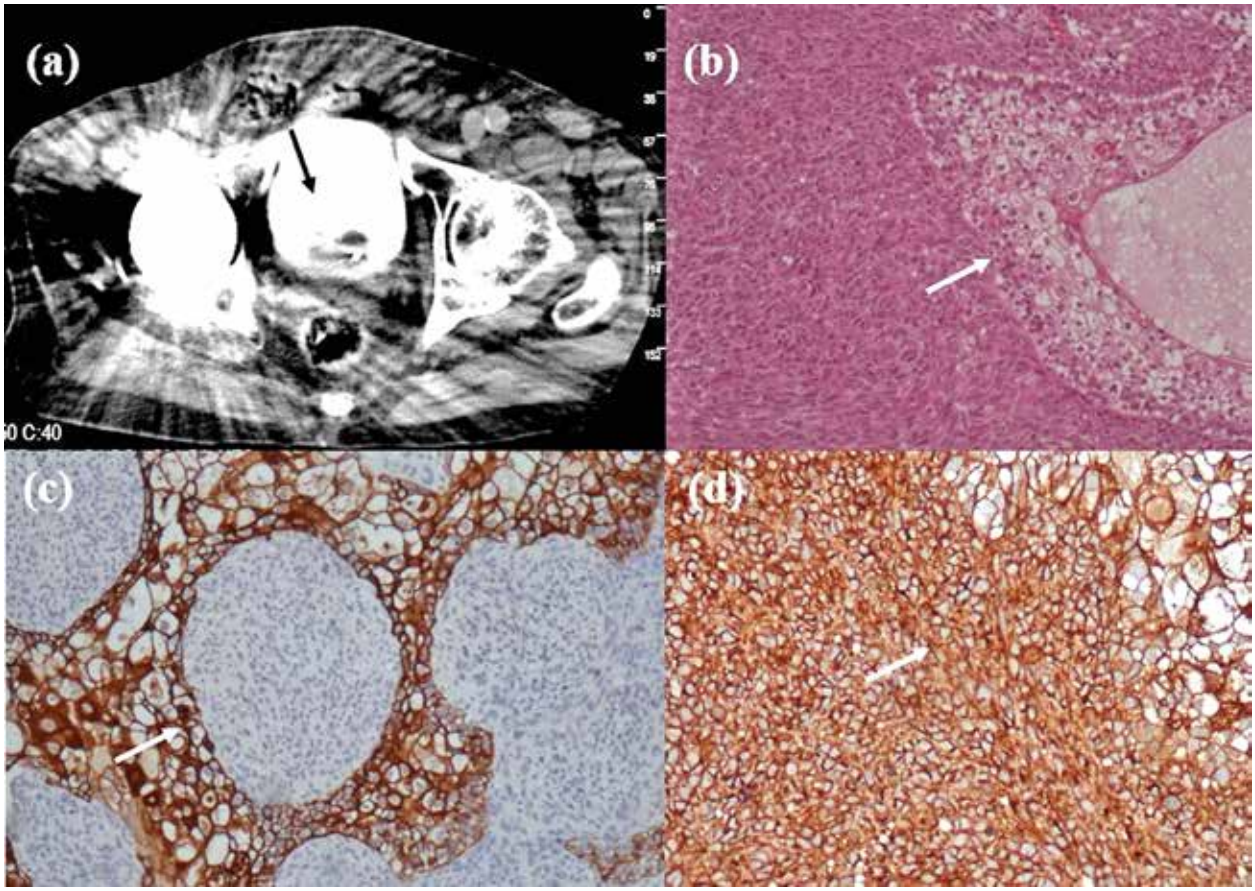

Fig 1. Radiologic and pathologic findings are summarized in the figure. **(a)** Mass is at the dome of the bladder, with 3 cm diameter, in computed tomography (arrow), **(b)** Tumor infiltration is slightly seen in mucosa with haematoxylin-eosin (HE x 20, arrow), **(c)** Adamantinoma like lesions were CD99+ and HMWK+ (arrow), **(d)** Tumor was PAS + (arrow).

cystoscopy. Tumor was occupying the whole anterior wall of the bladder with no papillary aspects. All tumor tissues were resected by TURBT. Early administration of mytomycin was performed in bladder by using urethral catheter, after TURBT. Pathology reported small rounded blue malignant cells without differentiation and loosely cohesive tumor cells with basophilic cytoplasms and highly polymorphic nucleuses. The tumor did not infiltrate the muscularis propria and was just infiltrating lamina propria. Additionally, there was a lot of typical and atypical mitoses and interestingly, wide necrotic fields which were like adamantinoma, involving intra cytoplasmic PAS (+) material (Fig 1b - d). These findings were complemented by an immunohistochemistry which was strong positive for the markers including CD99, vimentin, HMWK, PanCK, CK7, NSE, and WT-1. In view of these, adamantinoma like PNET of the bladder was diagnosed (Fig 1).

In clinical follow-up, re-cystoscopy and biopsy were performed in tumor resected area, six weeks after TURBT. Pathology reported that there was not any tumor cells in the resected biopsy materials. Control cystoscopy was performed in the 3rd, 6th and 9th month of surgery and there was recurrence and/or new tumor in bladder. Additionally, the patient has been followed-up by cross-sectional imaging of the chest, abdomen and pelvis by CT as this disease has been reported to metastasize to organs in these confines[1-3].

DISCUSSION

The PNET is a rare entity in elderly, and is a part of Ewing sarcoma family[3]. Although, characteristics of tumors are usually aggressive, these depends on tumor burden as well as having metastases[4].The accurate follow-up strategy of bladder's PNET has been still debate, because of its rarity. The exact diagnosis can be performed in pathological evaluations. However, the aggressive pattern of tumor may cause to metastasis and therefore, chemotherapy and/or radiotherapy may be needed[4]. In the present study, we introduced an extreme case of hematuria which was caused by adamantinoma like PNET in the bladder of an

83-year-old man. According to our best knowledge, he was the oldest patient who had PNET in bladder, in published literature.

Transitional cell carcinoma (TCC) is frequent in elderly patients, notably patients with smoking history[5,6]. European guidelines of urology on bladder cancers described diagnosis and treatment options of TCC as well as other histologic type of bladder cancers[7]. The differential diagnosis of the tumors can be made by pathological evaluations in which immunohistochemistry may be helpful. In our case, the tumor was positive for CD99, vimentin, HMWK, PanCK, CK7, NSE, and WT-1. Especially, positive staining with CD-99 was essential for diagnosis of PNET. Additionally, our case was positive staining with HMWK.

Recently, Tian *et al* reported a case series of PNET in bladder[8]. However, endometrial stromal carcinoma is rare and low grade variant of PNET, PNET should be kept in mind in case of bladder tumors, notably in non-smoker young patients.

Okada *et al* reported molecular diagnosis of PNET in bladder[5]. However, this may be easy for specific diagnosis method in PNET, and it is expensive. In our opinion, the molecular diagnostic kits can become cheaper by using more molecular methods. Therefore, accurate and easy diagnosis may come into question.

Rao *et al* reported fine-needle aspiration for diagnosis of PNET in bladder[1]. This method might lead to spread tumor into biopsy tract because of PNET has usually aggressive pattern. Furthermore, these clinical features need additional therapy modalities such as chemo and/or radiotherapies.

However, our case did not need any additional chemo and radiotherapy. It is a proven truth that mytomycin can reduce pTa low grade TCC of the bladder and not even pT1 TCC. There was no recurrence in our patient. However, prospective with larger sample, and long term follow-up studies are needed for evaluating recurrence, metastasis and progression, more accurately[9]. On the other hand, anti-coagulant drugs which the patient was using may lead to early hematuria, thus early diagnosis could be performed. Nonetheless, there was no recurrence during short-term follow-up. Our unique case was the oldest patient with PNET of bladder, and also PNET had adamantinoma like lesions, in published literature. In the light of our findings and literature, PNET in bladder can be diagnosed even up to the age of 83.

CONCLUSION

Bladder tumors usually cause hematuria, and rare type of tumors such as PNET should be kept in mind, notably in elderly patients. When early diagnosis and TURBT were performed with postoperative administration of mytomycin, additional treatment modalities may not be necessary. Nonetheless, bladder tumors which TCC and also rare diagnosed types such as PNET, need long-term follow-up for accurate evaluations.

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Case Report

Pilonidal Sinus of the Scrotum: A Rare Localisation

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ABSTRACT

Pilonidal sinus usually occurs in the sacrococcygeal area and can also be seen in other hairy areas. But scrotal location has not been reported previously. Here we report the first case of scrotal pilonidal sinus. A 21-year-old healthy male patient, presented to our urology department with the complaint of milky white discharge from the right hemiscrotum. He had no history of previous systemic and/or genital tuberculosis, epididymo-orchitis, sexually transmitted disease, scrotal trauma, surgery and urethral catheterization. Physical examination demonstrated milky white discharge from an orifice located in the right hemiscrotum. Microbiological investigations, urogenital ultrasonography and chest X-ray were normal. Scrotal exploration was decided to diagnose the clinical condition and 4 cm long fistula tract lying subcutaneously was excised from the right hemiscrotum. Pathologic examination demonstrated pilonidal sinus. Complete recovery was achieved by surgical excision without any complication. Scrotal pilonidal sinus must be kept in mind as one of the rare cause for scrotal discharge. Surgical excision is the best treatment option.

KEYWORDS: fistula, hemiscrotum, milky white discharge, urethral catheterization

INTRODUCTION

Pilonidal sinus is a long-standing chronic inflammatory condition. A sinus tract extends into subcutaneous tissue from a skin-lined orifice with hairs in the tract wall. Pilonidal sinuses usually occur in the sacrococcygeal area and also can be found in other ectopic sites like scalp, ear, brow, cervical subcutaneous region, axilla, interdigital clefts, anterior chest wall, nipple, umbilicus, suprapubic region, perineum, clitoris, anal canal, sole of foot, and amputation stumps[1]. To our knowledge, scrotal location is not reported before, and this is the first reported case of scrotal pilonidal sinus.

CASE REPORT

A 21-year-old healty male patient presented with the complaint of milky white discharge from the right hemiscrotum since one year. He had no history of previous systemic and/or genital tuberculosis, epididymo-orchitis, sexually transmitted disease, scrotal trauma or surgery, urethral catheterization and had never been traveled to a foreign country. Physical examination of the scrotum, testes and inguinal region was normal except milky white discharge from an orifice located in the right hemiscrotum. Microbiological investigations, urinary and genital ultrasonography and chest X-ray were normal. Scrotal exploration was decided. An angiocath (no. 20) was inserted from the scrotal orifice of the fistula as a guide and dissection was carried forward over the guide. Approximately 4 cm long fistula tract lying subcutaneously was excised from the right hemiscrotum (Fig 1). The right testis was not affected. Pathologic examination demonstrated pilonidal sinus lined by stratified squamous epithelium, showing chronic fibrosis and inflamation in the wall and few hair fragments in the lumen (Fig 2). The patient was discharged to home two days postoperatively without any complication. After six weeks standart follow up, the patient had no complaint and no recurrence was found.

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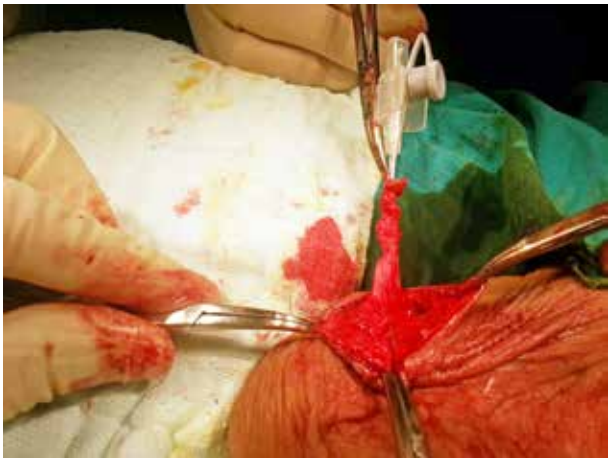

Fig 1: Subcutaneous fistula tract

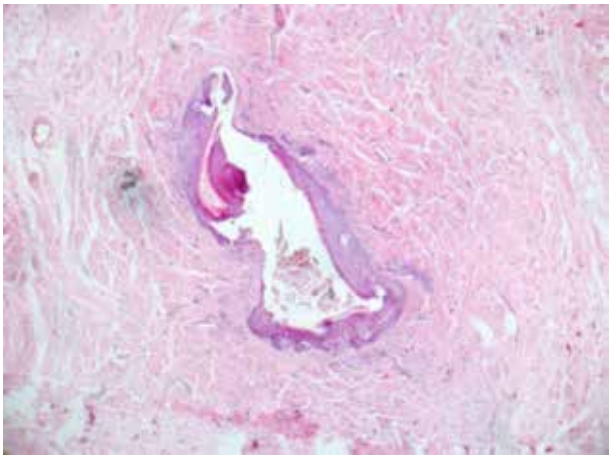

Fig 2: Pilonidal sinus lined by stratified squamous epithelium, showing chronic fibrosis and inflamation in the wall and few hair fragments in the lumen

DISCUSSION

Pilonidal sinus is a long-standing chronic inflammatory condition usually located in the sacrococcygeal area[2]. Pilonidal sinuses clinically present with pain, local infection and redness. Complication includes cellulitis and abscess formation[2]. Also malignant transformation may occur[3,4].

The origin of pilonidal sinus remains controverse. It may be congenital or acquired[5]. The present view is that the large majority of pilonidal sinuses have an acquired pathogenesis. The initiating event appears to be follicular hyperkeratosis with plugging, leading to retention of follicular products [6]. Also lack of hygiene on the affected area and penetration and growth of a hair in the subcutaneous tissue may cause acquired disease[2]. In our patient, frequent scrotal shaving may be a reason for trauma and consequent penetration of a hair into the subcutaneous tissue, which later cause pilonidal sinus.

Retention of follicular products results in infection and abscess formation; thus, the sinus tract usually forms to drain the abundant suppuration. In the rare cases without secondary infection, there is no opening onto the skin and pilonidal cyst may form[2]. Our patient presented with milky white discharge from right hemiscrotum since one year without pain and local infection. The opening on the skin was visible, but there was no hair projecting from the orifice. All microbiological and radiological investigations were normal.

Surgery is the main treatment option for pilonidal sinuses[7]. We performed surgical excision and complete recovery was achieved. After six weeks standart follow up, no recurrence was found.

CONCLUSION

Here we report the first case of scrotal pilonidal sinus. Pilonidal sinus should be considered an important but very rare differential diagnosis in case of scrotal discharge. Surgical excision is the best treatment option for scrotal pilonidal sinus.

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Case Report

Milky Pleural Effusion, A Rare Complication of Left Atrial Myxoma

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ABSTRACT

We report a rare case of bilateral chylothorax, associated with huge left atrial mass in a 45-year-old woman who presented with preoperative dyspnea, fever and weight loss. Transe esophageal echocardiography (TEE), gross, and microscopic features of the mass were consistent with myxoma. Biochemical analysis of bilateral effusion revealed chylothorax in pre - and post - operative periods. We conclude that myxoma-induced mitral stenosis and pulmonary hypertension should be included in the differential diagnosis of bilateral pleural effusion and chylothorax. In addition, pulmonary pressure should be monitored before and during diagnosis, in therapy of any effusion derived from myxoma.

KEY WORDS: bilateral pleural effusion, cardiac surgery, congestive heart failure, pulmonary embolization

INTRODUCTION

Chylothorax refers to the presence of fatty fluid with increased triglyceride levels in the pleural space, secondary to leakage from the thoracic duct or one of its main tributaries.[1] Chylothorax is a relatively uncommon disorder in cardiac surgery patients whose pathogenesis is divided into traumatic chylothorax and non-traumatic chylothorax, and the latter includes tumor, infection (virus, fungus, bacteria, tuberculosis, etc) [2-6]. Clinical symptoms of cardiac myxomas are often very confusing. Cevese found that the most common symptom associated with cardiac myxoma is congestive heart failure, followed by either systemic or pulmonary embolization[7]. Bjessmo described that, the patients may rarely present with symptoms mimicking mitral valve obstruction and pleural effusion[8]. Strambu reported a case of right plural effusion complicated by congestive heart failure[9] and Andrew found a case of left pleural effusion associated with heart failure[10]. Sanna related a case of plural effusion in myxoma to systemic disease[11]. Maldonado revealed that although chylothorax is typically classified as an exudative effusion but, transudates have been described in patients with lympho proliferative disease following surgery, following exposure to radiation in idiopathic cases, and in patients with concomitant illness such as cardiac or renal failure[12]. The thoracic duct is located in the superior mediastinum, to the left of the posterior wall of the esophagus, close to the aortic arch and to the left subclavian artery. In the neck, it has a lateral ascending course and an inferior rotation behind the first portion of the left subclavian artery where it connects to the left internal jugular vein.[13] During cardiac surgery, lymphatic channels may be disrupted in the region of patent ductus arteriosus (PDA), hiatus of diaphragm, esophagus near of aorta, the thymus, during encircling of IVC or SVC or near the origin of the internal thoracic artery, which is taken out as part of the operative procedure or neck dissection (endarterectomy), or surgery of retro mediastinal thyroid, blunt trauma or during thymectomy[14-19]. In non-traumatic case of chylothorax following cardiac pathology, increased ductal pressure as result of increase central venous pressure (thrombosis, tumor, heart failure, heart valve disease) or increasing lymph flow (heart failure) caused plural effusion and chylothorax as in obstructing mitral valve by myxoma[19-23].

CASE REPORT

A 54-year-old woman was admitted with a history of malaise, dyspnea, weight loss and non productive cough for the one year to the local state hospital. She had no history of any comorbid disease. One week

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prior to admission, the patient also had dyspnea even on slight activity. She was hospitalized with diagnosis of heart failure and her complaints were resolved after diuretic treatment. One week after discharge from the local hospital, she was admitted to our heart center with the same complaints. On physical examination, the heart rate was regular at 120 beats/min and blood pressure was 90/60 mmHg and she was orthopneic. Jugular veins were distended. Respiratory sounds were not audible on the lower portions of the lung fields and there was dullness to percussion in both bases posteriorly. Fine crepitating rales were also heard on the mid portions of the chest bilaterally and electrocardiographic findings consistent with huge left atrial mass and sever pulmonary hypertension. Chest X-ray revealed bilateral effusion. Pleural fluid analysis confirmed the chylous effusion (Fig 1). The patient was in respiratory distress. Jugular venous pressure was elevated to 18 cm of water, and pressure readings

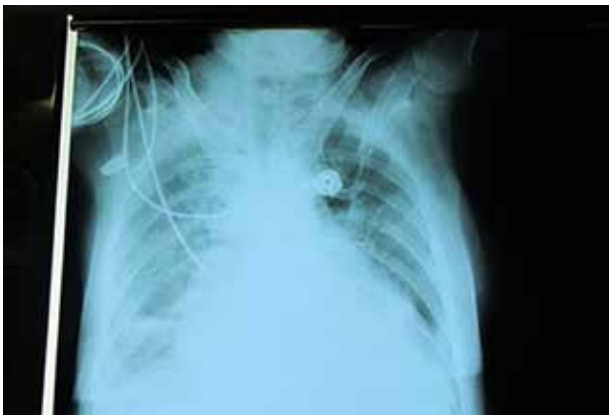

Fig 1: Chest X-ray revealed bilateral chylous effusion

showed prominent V waves. The carotid upstroke was brisk. Cardiac examination showed sternal lift and apical thrill. Auscultation revealed a soft S_1, an increased pulmonary component of S_2, and a grade 2/6 apical diastolic rumble without opening snap. Bilateral crackles were noted at mid-lung. A complete blood count revealed normocytic anemia (10 g/dL), and the results of a biochemical analysis were within normal limits. A chest radiograph revealed a bilateral pleural effusion (Fig 1). Electrocardiography showed sinus tachycardia (heart rate, 145 beats/min) and left atrial enlargement. Transesophageal echocardiography (TEE) showed huge left atrial mass (Fig 2) that caused mitral stenosis, an elevated mean gradient secondary to the mitral stenosis, and increased flow secondary to the tricuspid regurgitation. The valve itself was normal, as evidenced by a mobile leaflets and normal leaflet excursion. Analysis of the patient's sever tricuspid regurgitation (peak velocity, 45.3 m/s) showed severe pulmonary hypertension (pulmonary artery pressure,

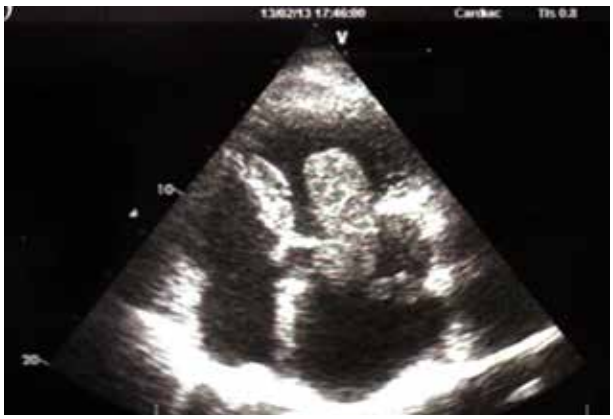

Fig 2: Transe thoracic echocardiography in four chamber view revealed huge myoma in the entrance of mitral valve

98 mmHg). The left ventricular ejection fraction was 55%. Over the course of the following days, her treatment included surgical resection of left atrial mass by open heart surgery (Fig 3) and tube thoracostomy drainage of the pleural effusion. A Gross inspection of the tricuspid valve did not reveal a specific underlying disease process. The drained fluid with milky color was tested biochemically in preoperative period and was found to contain chylomicrons (800 mg/dl) and triglycerides (245 mg/dl). The electrolyte content of

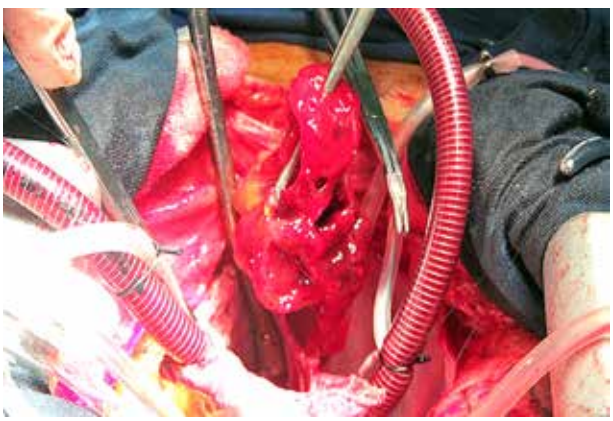

Fig 3: Intra operative view of myxoma in left atrium

chyle was similar to that of serum. The concentration of protein in chyle was 4.0 gm/dl. Chyle also contains 6000 white blood cells/ml, predominantly was lymphocytes. The patient's postoperative course was complicated by a milky left pleural effusion. It emerged on the first postoperative day (2000 ml), decreased gradually on the fifth postoperative day, and dissolved spontaneously one week after the operation. Biochemical analysis of effusion in post operative period also revealed its chylous content. Gross examination of the mass showed its grip shape and its pliable consistency (Fig 4). Microscopic evaluation revealed myxoma cells form rings, cords, and nests that are often closely associated with capillaries. The cells can also exist singly as

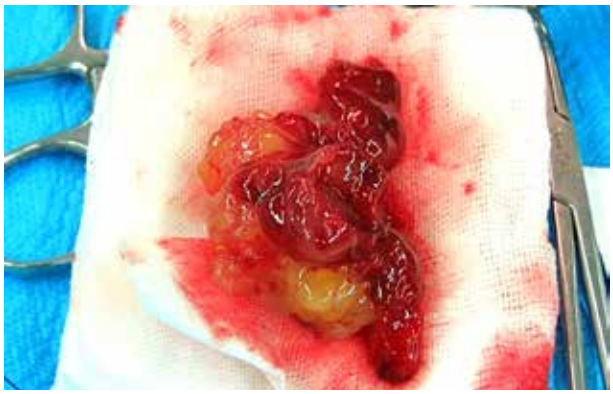

Fig 4: Gross pathology of myxoma

satellite cells in a myxoid stroma that is composed of variable amounts of proteoglycans, collagen, and elastin and that often contains lymphocytes, plasma cells, and histiocytes. These findings were consistent with myxoma. Myxoma-induced chylothorax" was designated after we ruled out all possible causes including chest trauma, lymphoma, lung cancer, tuberculosis, *etc*. She was given a low-fat, high-protein diet postoperatively. Echocardiographic data obtained during the following weeks, indicated only stable moderate regurgitation, without evidence of stenosis, and also showed significant improvement in the patient's pulmonary hypertension. The most recent echocardiogram, performed three month postoperatively, revealed a pulmonary systolic pressure of 40 mmHg. The patient was discharged to home on the 12th postoperative day.

DISCUSSION

As lymph vessels from the peritoneal cavity and lower body come together below the diaphragm, they give rise to the cisterna chyli, from which the thoracic duct originates. Duct passes with the aorta through the diaphragm and ascends to the subclavian vein. Mediastinal partway of lymph vessels predisposed to any injury of main duct or its normal or abnormal side's branches such as lymph chain in pathway of left internal mammary artery (Lima artery) or increase in pressure of duct associated with increase pressure in central vein as in myxoma-induced mitral stenosis[24]. Our case has two unique features: 1) pulmonary hypertension as a rare sequel of mitral stenosis-induced by myxoma, and 2) chylothorax as a sequel of severe pulmonary hypertension. Plural effusion associated with mitral stenosis has been identified previously, but the concurrent development of chylothorax with left atrial myxoma has not, to the best of our knowledge, been documented. The mechanism behind the development of chylothorax secondary to myxoma is related to increasing left atrial pressure consequence to mitral stenosis. Chylothorax in relation to underlying mitral stenosis was first described by Brenner *et al* in 1978[25] Previously, Benard *et al*[26] found drug-induced fibrosis of mitral valve associated with inflammation and consequent scarring of the pericardial serosal layer and constrictive pericarditis. If constrictive pericarditis is the responsible entity, chylothorax develops due to increased pressure in the lymphatic system, secondary to elevated central venous pressure. Another possible cause of chylothorax in our patient was elevated right-sided cardiac pressure. Brenner *et al* showed a correlation between right-sided heart failure secondary to valvular disease and the resultant development of chylothorax[25]. Our patient presented with pulmonary artery pressures of > 80 mmHg. Two months after the surgical resection of a myxoma, her pulmonary artery pressure dropped to 34 mmHg, with no recurrence of chylothorax. The postulate for the pathophysiologic mechanism is similar to that for other cases of increased right atrial pressure associated with elevated pressure in the subclavian vein that raises pressure in the lymphatic system[27]. Chylothorax and myxoma-mimicking mitral stenosis disease are both rare entities. Nevertheless, chylothorax development secondary to myxoma should be considered in patients who present with mitral stenosis-induced by myxoma and an increasing pressure of left atrium transferred to capillary pulmonary system and main pulmonary artery and right atrium. Increasing right atrial pressure transferred via right subclaveian vein to entrance of thoracic duct and raising its pressure. However, many patients with prolonged untreated mitral stenosis suffered from right heart failure, tricuspid regurgitation, pulmonary hypertension but incidence of chylothorax in these patients is exceedingly rare event. We suppose that the other associated conditions such as aberrant thoracic duct, congenital absence of valve in thoracic ducts may have a roll in the pleural chylous effusion in these rare cases[28], moreover, right cardiac function should be monitored before and during treatment of myxoma induced chylo thorax. Right heart failure increase central venous and lymph duct pressure and chylous leaks. Moreover, direct drainage of the lymph into the thoracic duct was observed in 10 cases out of a series of 589 injections of lung segments in adult cadavers in Riquit study[29]. Increased pulmonary pressure in these lung segments as in myxoma induced mitral stenosis may have a roll in chylous effusion. The thoracic lymphatic vessels are pulsating channels which drain actively the fluid of lung interstitial parenchyma and pleural cavities. Their unidirectional valves that avoid reflux of

contents, direct the current of fluid to the connection of thoracic duct to subclavian vein or to the thoracic duct itself by these pulsations. Absence of valves in thoracic duct in rare patients with increased left atrial pressure or elevated pulmonary pressure also cause increased because lymph flow and reflux and spontaneous rupture of micro vascular lymph duct in partial visceral pleura and effusion[30]. In Murakami study, seven patients with chylothorax and 30 healthy individuals (as the control group) underwent three-dimensional heavily and routine T2-weighted magnetic resonance scan (MRI). Morphological changes and diameters of the thoracic duct, chyloma display, and some dilated accessory lymph channels were evaluated and measured. The patients had a higher display rate of the entire thoracic duct and some accessory lymphatic channels, enlarged diameters and tortuous configuration of the thoracic duct, and existence of chyloma compared with the control group ($p < 0.05$)[31]. Seven leaks of the thoracic duct in five patients and five leaks of the parietal pleura in four patients were identified. However, the thoracic duct as a main collecting vessel of the lymphatic system is well known, whereas little is known about the intra thoracic tributaries of the thoracic duct, which are named, inter costal, mediastinal, and bronco mediastinal trunks. Injection of dye to intra thoracic organs permits visualization of thoracic duct tributaries. These tributaries appear located at unchanging levels. Lymph of intra thoracic organs may thus drain into the general circulation through the thoracic duct. The tributaries may represent a potential route for tumor cells metastasis in competent valve of thoracic duct butt. When incompetent due to valve insufficiency, they permit chylous lymph to backflow into the intra thoracic lymph nodes. Injury or increased pressure or over flow of lymph at this level may lead to intra thoracic chylous effusions. Murakami revealed that these findings allow the collecting vessels from the thoracic viscera to be divided into two pathways on each side: the anterior and posterior mediastinal trunks on the right side, and the superior and inferior mediastinal trunks on the left side. In addition to the four trunks, the superficial communicating vessel between the right and left sides is also drained from the superior mediastinal trunk[32].

CONCLUSION

A patient with left atrial myxoma that caused functional mitral stenosis presented with a chylous pleural effusion. Careful medical literature search found no other reports of myxoma-induced chylothorax caused by functional mitral stenosis and its sequels.

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Case Report

A Rare Complication of Rhinoplasty: A Case Report

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ABSTRACT

A 25-year-old man presented with nasal obstruction and nasal deformity was planned for open septo-rhinoplasty. In the immediately post operative period, he developed ptosis, fixation of the pupil and globe of the right eye and loss of vision. Condition did not improve even three months post-operatively. We present here, the possible causes of blindness and its literature review with regards to rhinoplasty.

KEY WORDS: blindness, nasal obstruction, orbital, septorhinoplasty

INTRODUCTION

Elective rhinoplasty is a common procedure worldwide. Although these have been several documented complications for this procedure[1]. Transient and permanent blindness as a complication post elective rhinoplasty has only been reported twice[2,3]. Vascular insult was proposed by Cheney *et al*[3] secondary to retrograde flow of vasoconstrictor agent in blood flow, as a result of forceful injection in the septal region.

CASE HISTORY

A 25-year-old man presented to the clinic with the complaint of nasal obstruction and nasal deformity. He had no previous significant medical or surgical history. He was planned for open technique of septorhinoplasty. Routine laboratory investigations were done which included Complete Blood Count (CBC), Prothrombin Time (PT), Partial Thromboplastin Time (PTT), differential count and blood urea and creatinine which were all in the normal range. He underwent the procedure under general anesthesia. Vasoconstrictor (1:100,000 Epinephrine with 1% Xylocaine) was injected for the sites of columellar incision and marginal incision and bilateral osteotomy sites and on the dorsum. An inverted V- columellar incision extending to bilateral marginal was done and flap elevated, hump resection done, spreader grafts were placed bilaterally following open septoplasty and bilateral low-low lateral osteotomy. Tip work with trans/intra and inter-domal sutures was done. Blood loss during the procedure was minimal and no complications were observed during the surgery. Mean blood pressure during the procedure was 50 mmHg. The patient was extubated following surgery and shifted to the recovery room.

In the recovery room, he was noticed to have fully dilated right pupil which were not reacting to light. There was normal functioning of the left eye. Immediate bedside ophthalmology consultation was done in the recovery room and the initial impression was possible local anaesthesia (LA) infiltration to the right orbital apex region with a recommendation for CT scan to rule out any possible bony defect or haematoma formation. The CT scan with contrast was done immediately with no clear abnormality in the orbital cavity or its borders. There was no evidence of intra-orbital or retrobulbar haemorrhage. After the patient was completely awake following general anaesthesia, it was observed that he had a fixed right globe, ptosis with mild peri-orbital ecchymosis. He did not complain of pain. There was no light perception, the conjunctiva and cornea were both clear. Fundal examination was normal. Laboratory investigation were repeated to look for any abnormality including

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CBC, PT, PTT, differential count and International Normalized Ratio (INR) with no significant changes. A neurology consultation was also taken and suggested an MRI and MRV which was done the following day. MRI showed possible right thrombophletitis of cavernous sinus plus engorgement of right superior ophthalmic vein (Fig 1). The neuro-ophthalmologist was consulted and he diagnosed the case as right orbital apex syndrome (OAS) due to possible right

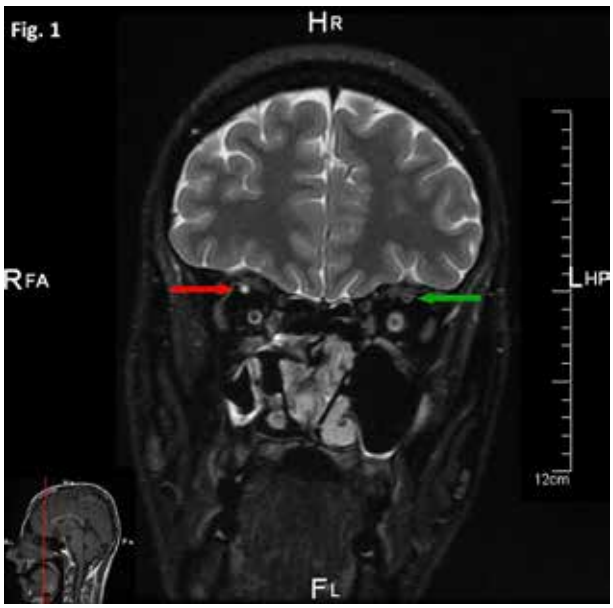

Fig 1: MRI Scan shows obstruction in the vessel on the affected side (red arrow) as compared to the normal vessel as the opposite side (green arrow).

cavernous sinus thrombophletitis possibly during forceful injection during infiltration.

Immediate post-operatively the patient was started on IV cefuroxime 2 gm which was changed to oral in two days and IV Hydrocortisone 250 mg every six hour for 24 hours and aspirin 80 mg tablets. The neurologist and neuro-ophthalmologist could not correlate the cause of the complication to any surgical step. The surgeon had not done any new technique or experienced anything unusual during the procedure. In the latest examination three months post-op, the patient still had complaint of loss of vision and ptosis of right eye with minimal to no changes of his ophthalmic findings from the previous visit, though he was very happy with the shape of his nose. He still has no perception of light in the right eye with 6 mm non-reactive pupils and severe optic neuropathy.

DISCUSSION

Cavernous sinus lie on the side of the body of sphenoid, extending from the apex of petrous part of the temporal bone to the medial end of the superior orbital fissure. The following cranial nerves lie in its lateral wall: oculomotor (3rd), trochlear (4th), ophthalmic and maxillary division of trigeminal nerve V. Internal carotid artery; abducent nerve and carotid sympathetic plexus lie within the cavity of cavernous sinus. Cavernous sinus have tributarier and communications. Anteriorly, ophthalmic veins (connect it with the facial veins in the face) and the sphenoparietal sinus. Posteriorly, superior petrosal sinus (connected it with transverse sinus) and inferior petrosal sinus (connects it with the internal jugular veins) medially anterior and posterior intercavernous sinuses (connect the 2 cavernous sinuses). Superiorly, it is connected to superficial middle cerebral vein and cerebral veins. Inferiorly, it is connected to emissary veins through the cerebral canal and foramen ovule. The blood flow in all the tributarier and communicators are reversible due to absence of venous valves. Cavernous sinus communicate to midface veins via (1) superior ophthalmic vein and deep facial veins, (2) pterygroid plexus and emissary veins through the foramen ovule.

The complete orbital apex syndrome (OAS) is the association of lesion of the 3rd, 4th and ophthalmic division of the 5th cranial nerve (V1) with optic neuropathy. Proptosis is common. The superior orbital fissure syndrome (SOFS) and cavernous sinus syndrome (CSS) can produce similar clinical picture. Orbital apex, superior orbital fissure and cavernous sinus are anatomically close to each other so syndromes have been used to describe anatomical location of disease process. However, the etiology, diagnostic evaluation and management are similar and hence grouped under orbital apex syndrome. The causes of OAS are described in Table 1.

Table 1: Classification of the causes of orbital apex syndrome

Inflammatory	**Infective**
Sarcoidosis	Fungi, aspergillosis,
Systemic lupus erythematosis	mucormycosis
Wegener's granulomatosis	Bacteria-streptococcus,
Tolosa Hunt Syndrome	staphylococcus, anaerobes,
Giant Cell Arteritis	actinomycus M. Tb, T. Pallidum
Thyroid orbitopathy	Viruses – herpes zoster
Neoplastic	**Iatrogenic Traumatic**
Head & neck tumors	Sino-nasal surgery
Neural tumors – NF	Orbit/facial surgery
Metastasis	Traumatic
Haematological	
Perineural invation	
Vascular	**Others**
Carotid cavernous aneurysm	mucocele
Carotid cavernous fistula	
Cavernous sinus thrombosis	

There is no definitive documented cause for all the signs and symptoms that have been encountered in this particular case. J Awad *et al*[4] postulated that when epinephrine was injected under pressure into the tissue surrounding the inferior turbinate, there will be retrograde flow through the anterior ethmoidal artery into the ophthalmic artery, which causes likely vasospasm of the end arteries to the optic nerve and retina. This hypo perfusion induces the patient's optic neuropathy and unfortunately there is no treatment available in the late stages, even with corticosteroids and vasodilators as it is an ischemic (not an inflammatory) cause for the patient's visual loss and therefore, corticosteroids will not help. The most common probable reasons have been involvement of the retinal artery or the caveneous sinus[5,6]. Cavernous sinus involvement is through the possibility of retrograde flow of the epinephrine during forceful injection through the valve less angular veins and the ophthalmic veins to the cavernous sinus which could lead to cavernous sinus thrombosis or vasoconstriction in the venous system which would in turn lead to hypo-perfusion in the arterial system.

Elective rhinoplasty is a common procedure. Although, there have been several documented complications for this procedure[1]. Blindness as a complication post elective rhinoplasty has only been reported once[2]. Vascular insult was proposed by Cheney *et al*[3] secondary to retrograde flow of vasoconstrictor agent in blood flow as a result of forceful injection in the septal region.

Dubach *et al*[7] showed histologically that forceful infiltration will flow into the blood vessels and not be restricted to subperichondrial plane as intended by hydrodissection.

In our case, forceful injection for hydrodissection could have leaked into the vascular channels. This has caused narrowing of the cavernous sinus (Fig. 2). Another contributing factor is the hypotensive anaesthesia during the surgery. This theory has been documented by MRV which showed an element of venous involvement in the superior ophthalmic vein and cavernous sinus. This is the first case in literature documented by MRV. Although all measures were taken by anti-inflammatory and anti-coagulant therapy, the sequels of vascular insult cannot be avoided. Unfortunately, it is an irreversible condition. A subclinical cavernous sinus thrombophelbitis prior to surgery however, could not be ruled out.

CONCLUSION

This case is a result of vascular insult as evident by MRV. In contrast to complications arising from direct mechanical trauma, vascular problems may be very difficult to prevent or predict. However, it is reasonable to make the following recommendations. (1) vasoconstrictive agents should be used in as small doses as possible; (2) the injection of vasoconstrictor should be performed slowly with low pressure; (3) hydrodissection using normal saline instead of vasoconstrictive agents; (4) the patient should be closely observed in the postoperative period for at least 24 hours; 5) blindness, although very rare, should be informed in the consent for septhorhinoplasty.

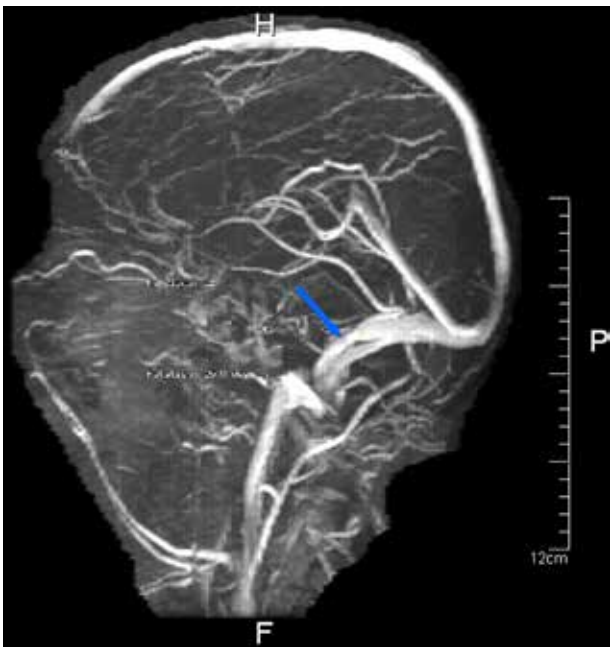

Fig 2: MRV shows the typical bead sign/hour glass appearance of the superior ophthalmic vein due to surrounding soft tissue edema.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2016; 48 (4) : 357 - 360

Atmospheric Concentration of Polychlorinated Dibenzo-P-Dioxins, Polychlorinated Dibenzofurans (PCDD/Fs) and Dioxin-Like Polychlorinated Biphenyls (dl-PCBs) at Umm-Al-Aish Oil Field-Kuwait

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A sampling campaign was carried out to assess the impact of the oil field activities on the concentrations of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (dl-PCBs) in ambient air at Umm Al-Aish oil field in northern Kuwait. Sixteen samples were collected from March 2014 to January 2015. The concentrations of ΣPCDD/Fs were relatively high (33.6-586 fg I-TEQ/m^3; median: 94.7 fg I-TEQ/m^3; 31.2 to 516 fg WHO-TEQ_{2005}/m^3; median: 83.7 fg WHO-TEQ_{2005}/m^3) compared to those of dl-PCBs (3.9-36.8 WHO-TEQ_{2005}/m^3; median 9.9 WHO-TEQ_{2005}/m^3). A unique PCDD/F profile that was not previously reported was found. Further investigations should be conducted to establish whether the dioxin profile found in this study is specific for the desulfurization facility located in the study area or from oil flaring in the oil fields located upstream of the study area. The findings suggest that the oil field activities have a significant impact on the PCDD/F concentration in ambient air but a low or negligible influence on dl-PCBs' levels.

Schistosomal Appendicitis in Kuwait A 5-Year Study

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Background: Appendicular schistosomiasis is an unusual etiology of acute appendicitis, which has been reported in countries endemic in schistosomiasis, such as sub-saharan Africa and South America. Nowadays, due to globalization, this disease has been diagnosed in non-endemic countries. Kuwait is a country possessing a larger percentage of foreigners than national citizens. Therefore, several cases of schistosomal appendicitis were found.

Method: The clinicopathological records of all patients that underwent appendectomy during January 2007 and December 2011 were recorded from the archives of Al-Adan Hospital in Kuwait. All cases of schistosomal appendicitis were retrieved and the histopathologic slides reconfirmed by the histopathologist.
Results: During the 5-year study period, 3012 appendectomies were performed and 8 schistosomal appendicitis were found. They were all Egyptian males that were admitted for a clinical suspicion of acute appendicitis. The age ranged between 24 and 42 years, with a mean age of 32.75 years. All cases showed histological features of acute or acute suppurative inflammation, with ova seen in the vasculature of all layers of appendicular wall.
Conclusion: Although schistosomiasis is a rare causative agent of acute appendicitis, this however can't be confirmed until histological evaluation. Therefore, adequate follow up postoperatively is necessary to insure eradication of the disease and to prevent further serious consequences.

Detection of Trichomonas Vaginalis in Prostate Tissue and Serostatus in Patients with Asymptomatic Benign Prostatic Hyperplasia

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Background: Despite a worldwide common and progressive nature of benign prostate hyperplasia (BPH) in older men, no association has been observed between a causative pathogen and other etiology so far.
Methods: In this study, we investigated a causative association of Trichomonas vaginalis, a flagellate protozoan parasite, in 171 BPH cases presenting without symptoms of prostatitis at a surgical outpatient clinic in Kuwait. We detected T. vaginalis DNA by polymerase chain reaction (PCR) and T. vaginalis antigen by immunocytochemistry (ICC) in the prostate tissue of these cases. A total of 171 age-matched controls with no urinary tract symptoms were also included in the study. A detailed information regarding the sexual history and sexually transmitted infections (STIs) was enquired from all the enrolled subjects.
Results: We detected T. vaginalis DNA and T. vaginalis antigen in 42 (24.6 %) and 37 (21.6 %) of the 171 BPH cases respectively in their prostate tissue. Both these assays showed a very good agreement and statistically no significant difference in their sensitivities and specificities. A relatively higher seropositivity rate for antibodies to T. vaginalis was detected in BPH cases (53 of 171 cases, 31.0 %) than in the control group (26.9 %) [p: 0.19] and both were higher than in earlier reports but no significant association was observed between BPH and T. vaginalis serostatus. However, a greater proportion of seroreactive BPH cases had high IgG2 antibody absorbance score than in the control group (p:0.000). Furthermore, no significant association was observed between T. vaginalis seropositivity and presence of T. vaginalis DNA in the prostate tissue.
Conclusions: Our study documents T. vaginalis DNA and T. vaginalis antigen in 24.6 and 21.6 % respectively in the prostate tissue of the BPH cases. We also detected a relatively higher seropositivity rate for antibodies to T. vaginalis both in the BPH cases and in normal control group, 31 and 26.9 % respectively but no significant association was observed between BPH and T. vaginalis serostatus or presence of T. vaginalis DNA in the prostate tissue. Further epidemiological and case-controlled studies are needed to focus on local response to chronic asymptomatic retention of T. vaginalis in prostate tissue in the development of benign prostate hyperplasia.

The Oral-Systemic Disease Connection: A Retrospective Study

Joseph BK[1], Kullman L[2], Sharma PN[3]
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[2]Department of Dental Medicine, Karolinska Institute Stockholm, Solna, Sweden
[3]Health Sciences Center, Kuwait University, P.O. Box: 24923, Safat, 13110, Kuwait, Kuwait

Clin Oral Investig 2016; 20:2267-2273. Epub 2016 Feb 3

Objectives: The study aimed at determining the association between oral disease and systemic health based on panoramic radiographs and general health of patients treated at Kuwait University Dental Center. The objective was to determine whether individuals exhibiting good oral health have lower propensity to systemic diseases.
Materials And Methods: A total of 1000 adult patients treated at Kuwait University Dental Center were randomly selected from the patient's records. The general health of patients was assessed from the medical history of each patient recorded during their visit to the clinic. The number of reported diseases and serious symptoms were used to develop a medical index. The oral health of these patients was assessed from panoramic radiographs to create an oral index by evaluating such parameters as caries, periodontitis, periapical lesions, pericoronitis, and tooth loss.
Results: In a total of 887 patients, 43.8 % had an oral index between 3 and 8, of which significantly higher (62.1 %) patients were with medical conditions compared to those without (33.2 %; $p < 0.001$). The Spearmans's correlation (rho') revealed a positive correlation (rho' = 0.360, p 0.001) between oral and medical index. Partial correlation, while controlling demographics, gender, nationality, and age, also showed a significant positive correlation ($p < 0.001$) between medical and oral index.
Conclusions: The findings of this study showed a significant association between oral health and general health and confirmed the findings of previous reports as regards the existing correlation between dental infections and medical disorders. These results are not indicative of a causal relationship when the diagnosis of oral disease was based primarily on radiographic findings. Future research needs to include prospective clinical and interventional studies.
Clinical Relevance: The significance of the oral-systemic disease connection highlights the importance of preventing and treating oral disease which have profound medical implications on general health.

Awareness of Mouth Cancer Among Adult Dental Patients Attending the Kuwait University Dental School Clinic

Joseph BK[1], Ali MA[2], Sundaram DB[2]
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[2]Department of Diagnostic Sciences, Faculty of Dentistry, Kuwait University, P.O. Box: 24923, 13110, Safat, Kuwait

J Cancer Educ. 2016 Sep 8. [Epub ahead of print]

In Kuwait, the age-standardized incidence rate (per 100,000) for oral cancer is 1.5 and the mortality rate is 0.4. Early detection of oral cancer combined with appropriate treatment greatly improves the chances of cure and the quality of life. However, little is known about patient awareness of this disease and the ability to identify early signs, particularly among high-risk groups. Hence, the aim of this study is to assess dental patients' awareness and knowledge of mouth cancer and beliefs and perceptions about risk factors. A self-administered questionnaire was used to collect information from a convenience sample of outpatients attending the dental admission clinic. The questionnaire included questions to ascertain

information on socio-demographic characteristics, knowledge of risk factors, and signs of oral cancer as well as sources of information regarding the same. Data were analyzed using the Statistical Package for the Social Sciences for Windows 19.0. A total of 160 questionnaires were distributed out of which 136 completed questionnaires were returned and used for the study. The mean knowledge score for oral cancer risk factors was found to be 5.2 ± 2.7 out of ten while that of signs and symptoms was 3.4 ± 2.7 out of eight. When the knowledge of risk factors of oral cancer was taken into consideration along with variables, significant difference was seen only in sex with women having better knowledge ($p = 0.03$). Knowledge about signs and symptoms of oral cancer revealed a highly significant difference with the level of education ($p = 0.03$). Family, friends, and colleagues were mentioned as the main source of information regarding oral cancer. Our findings suggest that knowledge regarding oral cancer risk factors, signs, and symptoms was found to be lacking among the dental patients which emphasizes the need for patient education at the dental centers as well as public awareness programs.

Serotype Distribution and Penicillin-Non-Susceptibility of Streptococcus Pneumoniae Causing Invasive Diseases in Kuwait: A 10-Year Study of Impact of Pneumococcal Conjugate Vaccines

Mokaddas E[1], Albert MJ[1]
[1]a Faculty of Medicine, Department of Microbiology, Kuwait University, Jabriya, Kuwait

Expert Rev Vaccines. 2016 Oct;15(10):1337-45. doi: 10.1080/14760584.2016.1198698. Epub 2016 Jun 24

Objectives: The impact of PCV7 and PCV13 on pneumococcal infections in Kuwait is not known. Therefore we evaluated the impact on pneumococcal serotype distribution and penicillin-non-susceptibility in invasive infections in Kuwait.
Methods: Children < 2 y were given PCV7 from Aug 2006 to Jul 2010 (period I), and PCV13 from Aug 2010 to Jul 2013 (period II) with a pre-vaccination period from Aug 2003 to Jul 2006. Serotype and penicillin-non-susceptibility of blood and cerebrospinal fluid isolates from all ages were determined.
Results: In <2 y old children, even with a small number of infections, a drop in PCV7 serotypes was evident after vaccination. For all age groups combined, in the pre-vaccination period, PCV7, PCV13, PCV13 non-PCV7 serotypes and penicillin-non-susceptibility constituted 53.2%, 72.6%, 19.4% and 6.5% of the isolates respectively. PCV7, PCV13 non-PCV7 serotypes and penicillin-non-susceptibility changed to 32.7%, 28.2% and 7.3% (period I) and 6.6%, 22.2% and 8.9% (period II).
Conclusions: Vaccines reduced invasive infections due to PCV7 serotypes.

Draft Genome Sequences of Five Clinical Strains of Brucella Melitensis Isolated from Patients Residing in Kuwait

Khan MW[1], Habibi N[1], Shaheed F[1], Mustafa AS[2,3]
[1]OMICS Research Unit, Research Core Facility, Health Sciences Centre, Kuwait University, Kuwait
[2]OMICS Research Unit, Research Core Facility, Health Sciences Centre, Kuwait University, Kuwait abusalim@hsc.edu.kw
[3]Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

Genome Announc 2016 Nov 3; 4(6). pii: e01144-16. doi: 10.1128/genomeA.01144-16

Human brucellosis is a neglected and underrecognized infection of widespread geographic distribution. Brucellosis is present on all inhabited continents and endemic in many areas of the world, including Kuwait and the Middle East. Here, we present draft genome assemblies of five Brucella melitensis strains isolated from brucellosis patients in Kuwait.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2016; 48 (4) : 361 - 373

14th Annual world congress on **Insulin Resistance, Diabetes & Cardiovascular disease**
Dec 1 - 3, 2016
United States / California / Los Angeles
Contact: Kaley Diep, Executive Assistant, Metabolic Endocrine Education Foundation (MEEF)
Phone: 818-342-1889; Fax: 818-342-1538
Email: admin@wcir.org

2nd International Congress on **Neuro-Immunology & Therapeutics**
Dec 1 - 3, 2016
Georgia / Atlanta
Contact: Jennifer Jones, Omics International
Phone: 888-843-8169; Fax: 650-618-1417
Email: neuroimmunology@conferenceseries.net

Emergency Skills in **Oral & Maxillofacial Surgery**
Dec 1 - 3, 2016
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

19th International Union against **Sexually Transmitted Infections** Asia-Pacific Conference
Dec 1 - 3, 2016
Japan / Okayama
Contact: Administrative Secretariat, Med-Gakkai
Email: 19iusti@med-gakkai.org

2016 Best of **Oncology East** Conference
Dec 2, 2016
Canada / Ontario / Toronto
Contact: Bianca Vasile, Event Coordinator, Oncologyeducation.Com
Email: Bianca@Oncologyeducation.Ca

2016 **Vitiligo** International Symposium
Dec 2 - 3, 2016
Italy / Rome
Contact: Organizing Secretariat, Quality Congress
Phone: 011-39-6-6651-4670
Email: info@vis2016.org

9th World Congress on **Prevention of Diabetes** & its complications (WCPD9)
Dec 2 - 4, 2016
Georgia / Atlanta
Contact: WCPD9
Fax: 011-20-2-2671-8421
Email: info@wcpd9.com

12th Annual **Liver Transplantation** Symposium
Dec 3, 2016
United States / Pennsylvania / Hershey
Contact: Department of Continuing Education, Pennsylvania State University
Phone: 717-531-6483; Fax: 717-531-5604
Email: continuinged@hmc.psu.edu

17th International association for the study of **Lung Cancer** (IASLC) World conference on lung cancer
Dec 4 - 7, 2016
Austria / Vienna
Contact: Pia Hirsch, Iaslc
Email: pia.hirsch@iaslc.org

One day essentials - **Ophthalmology**
Dec 5, 2016
United Kingdom / London
Contact: Conferences, Royal College of General Practitioners
Phone: 011-44-20-3188-7658
Email: rcgpconferences@rcgp.org.uk

2016 Emirates Society of **Emergency Medicine** Scientific Conference
Dec 7 - 10, 2016
United Arab Emirates / Dubai
Contact: Kris Olarte, Mci Middle East
Phone: 011-971-4-311-6300; Fax: 011-971-4-311-6301
Email: esem@mci-group.com

The 7th **Anesthesia and Critical Care** conference
Dec 8 - 10, 2016
Kuwait
Venue: Courtyard Marriott Alraya, Kuwait
Website: www.accc2016.com
Contact: Organizer, Medconf. Mobile: +965 99976664
Email: info@medconfevents.com

16th International forum on **Mood & Anxiety Disorders**
Dec 8 - 10, 2016
Italy / Rome
Contact: Publi Creations
Phone: 011-377-9797-3555;
Fax: 011-377-9797-3550
Email: ifmad@publicreations.com

Musculoskeletal **Ultrasound**
Dec 9 - 11, 2016
Belgium / Brussels
Contact: Medipoint
Phone: 011-32-5140-7674

Paediatric Inflammatory Bowel disease study day
Dec 9, 2016
United Kingdom / London
Contact: Academy for Paediatric Gastroenterology
Phone: 011-44-77-8591-4542
Email: query@a-p-g.co.uk

Update on **IV Fluids**
Dec 11-14, 2016
Italy / Rome
Contact: Marie-Rose Andre, Secretary, Erasme Hospital Intensive Care Department
Phone: 011-32-2-555-3380
Fax: 011-32-2-555-4555
Email: secrjlv@ulb.ac.be

2016 Current concepts in **Joint Replacement** Winter meeting
Dec 14 - 17, 2016
United States / Florida / Orlando
Contact: Current Concepts Institute
Phone: 216-295-1900
Fax: 216-295-9955
Email: info@ccjr.com

5th Emirates international **Urological** conference
Dec 15-17, 2016
United Arab Emirates / Dubai
Contact: Shilpa Alakkal, Meeting Minds Experts
Phone: 011-971-4-427-0492
Email: urology@meetingmindsdubai.com

6th International **Oncoplastic Breast Surgery** symposium
Dec 16 - 18, 2016
Thailand / Bangkok
Contact: Secretariat Office, Thailand Section of The International College of Surgeons
Phone: 011-66-81-701-8345
Fax: 011-66-2-950-7423
Email: iopbs.congress@gmail.com

2017 Asia **PCR** Singapore Live
Jan 19 - 21, 2017
Singapore / Singapore
Contact: Europa Organisation
Phone: 011-33-5-3445-2645
Email: europa@europa-organisation.com

Autism, ADHD & developmental disabilities through the lifespan Hawaiian cruise
Jan 21- 28, 2017
United States / Hawaii / Honolulu
Contact: Continuing Education
Continuing Education, Inc
Phone: 800-422-0711
Email: registrar@continuingeducation.net

Arrhythmias & the Heart: A cardiovascular update
Jan 23 - 27, 2017
United States / Hawaii / Big Island
Contact: Charlene Tri, Mayo Clinic
Phone: 800-283-6296
Email: ctri@mayo.edu

Basic techniques in **Arthroscopic Surgery**
Jan 24 - 25, 2017
United Kingdom / London
Contact: Education
Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Intermediate skills in **Laparoscopic Surgery**
Jan 24 - 25, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

24th International symposium on **Pancreatic & Biliary Endoscopy**
Jan 26 - 29, 2017
United States / California / Los Angeles
Contact: Office of CME
Cedars Sinai Medical Center
Phone: 310-423-5548
Email: cme@cshs.org

Advanced **Arthroscopic Knee**
Jan 26 - 27, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Reconstructive Techniques in **Urology**
Jan 30, 2017
United Kingdom / London Surgery, Urology
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: Education@Rcseng.Ac.Uk

19th International Conference on **Dialysis** / 2017 Advances in kidney disease
Feb 1 - 3, 2017
United States / Nevada / Las Vegas
Contact: Renal Research Institute
Phone: 212-331-1700; Fax: 212-331-1774

Operative skills in **Neonatal & Paediatric Surgery**
Feb 1- 2, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

3rd Seminar on **Tendon Transfers** of the upper limb
Feb 2 - 4, 2017
Greece / Thessaloniki
Contact: Premium Congress & Social events solutions
Phone: 011-30-23-1021-9407
Email: premium.conf@gmail.com

Renal Pathology for the Nephrologist
Feb 2 - 3, 2017
United Kingdom / London
Contact: Miss Anjli Jagpal, Course organiser, Imperial College London
Email: a.jagpal@imperial.ac.uk

Renal Pathology for the **Nephrologist**
Feb 2 - 3, 2017
United Kingdom / London
Contact: Miss Anjli Jagpal, Course Organiser, Imperial College London
Email: A. Jagpal@Imperial.Ac.Uk

2017 International symposium on **Endovascular Therapy**
Feb 4 - 8, 2017
United States / Florida / Hollywood
Contact: Complete conference management
Phone: 888-334-7495 (Toll Free) Or 305-279-2263
Fax: 305-279-8221
Email: Questions@Ccmcme.Com

Head and Neck **MRI**
Feb 6 - 10, 2017
Austria / Vienna
Contact: Walter Rijsselaere, Erasmus MRI Course
Email: walter.rijsselaere@uzbrussel.be

Quantitative MRI in White matter disorders
Feb 7 - 10, 2017
Canada / British Columbia / Vancouver
Contact: International Society for Magnetic Resonance in medicine
Email: info@ismrm.org

2017 Paris International **Shoulder** Course
Feb 9 - 11, 2017
France / Paris
Contact: Eventime Group
Phone: 011-33-4-9194-5472; Fax: 011-33-4-9158-5494
Email: contact@paris-shoulder-course.com

3rd Asia - Australia congress on controversies in **Ophthalmology**
Feb 9 - 12, 2017
South Korea / Seoul
Contact: Natalie Ross, Comtecmed
Phone: 011-972-3-566-6166
Email: cophyaa@comtecmed.com

7th Emirates **Diabetes & Endocrine** congress
Feb 16 - 18, 2017
United Arab Emirates / Dubai
Contact: Kris Olarte, MCI Middle East
Phone: 011-971-4-311-6300; Fax: 011-971-4-311-6301
Email: edec@mci-group.com

1st International Conference on **Zika Virus**
Feb 22 - 25, 2017
United States / District of Columbia / Washington
Contact: Conference, Secretariat, Target Conferences
Phone: 972-3-517-5150
Email: zika@target-conferences.com

2017 International **Stroke** conference
Feb 22 - 24, 2017
United States / Texas / Houston
Contact: American Heart Association
Phone: 888-242-2453 (Us) Or 214-570-5935
Email: sessionsadmin@heart.org

31st International **Papillomavirus** conference
Feb 28 - Mar 4, 2017
South Africa / Cape Town
Contact: Hpv 2017 Secretariat, Kenes International
Phone: 011-41-22-906-9160
Email: hpv2017@kenes.com

20th International Society of **Dermatopathology** (ISDP) Joint Meeting
Mar 1 - 2, 2017
United States / Florida / Lake Buena Vista
Contact: Diana Baughman, Manager, ISDP
Phone: 650-726-5481; Fax: 650-726-5481
Email: intsocdp@sbcglobal.net

Operative skills in **Urology**: Modules 1 & 2
Mar 1 - 2, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Stoller: **Musculoskeletal imaging** tutorial & mini-fellowship
Mar 1 - 3, 2017
United States / Nevada / Las Vegas
Contact: Administrator, CME Science
Phone: 650-440-4424
Email: info@cmescience.com

2017 University of British Columbia (UBC) **Whistler Anesthesiology** Summit
Mar 2 - 5, 2017
Canada / British Columbia / Whistler
Contact: Lindsay Callan, UBC CPD
Phone: 604-875-5101, Fax: 604-875-5078
Email: cpd.info@ubc.ca

27th Annual Australasian **Gynaecological Endoscopy & Surgery** Society Limited Scientific meeting
Mar 2 - 4, 2017
Australia / Sydney
Contact: YRD Event Management
Phone: 011-61-7-3368-2422
Fax: 011-61-7-3368-2433
Email: conferences@ages.com.au

4th International Conference on **Nutrition & Growth**
Mar 2 - 4, 2017
Netherlands / Amsterdam
Contact: Rachel, Kenes Group
Phone: 011-41-22-908-0488
Email: ngc@kenes.com

6th International Conference & Exhibition on **Cell & Gene Therapy**
Mar 2 - 3, 2017
Spain / Madrid
Contact: Angelica Kenova, Conferenceseries Lic
Phone: 650-268-9744; Fax: 650-618-1414
Email: celltherapy@conferenceseries.com

Care of the **Critically Ill** Surgical Patient
Mar 2 - 3, 2017
United Kingdom / London S
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Care of the **Critically Ill** Surgical Patient
Mar 2 - 3, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Microvascular Head & Neck Reconstruction course
Mar 3 - 4, 2017
Canada / Ontario /Toronto
Contact: Continuing Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719
Email: info-ent1214@cepdtoronto.ca

Practical **Ophthalmology** for the Non-Ophthalmologist
Mar 4, 2017
Canada / British Columbia / Vancouver
Contact: Continuing Professional Development, University of British Columbia
Phone: 604-875-5101
Fax: 604-875-5078
Email: cpd.info@ubc.ca

15th International Congress on **Targeted Anticancer Therapies**
Mar 6 - 8, 2017
France / Paris
Contact: Maureen De Graauw, Congress by Design
Phone: 011-31-8-8089-8101
Email: tat@congressbydesign.com

7th World Congress on **Women's Mental Health**
Mar 6 - 9, 2017
Ireland / Dublin
Contact: Colm O'grady, Congress Sponsorship, Conference Partners Ltd.
Phone: 011-353-87-223-3477
Email: Colm@Conferencepartners.Ie

18th Annual **Hernia Repair**
Mar 8 - 11, 2017
Mexico / Cancun
Contact: American Hernia Society
Phone: 866-798-5406; Fax: 303-771-2550
Email: contact@americanherniasociety.org

9th International DIP Symposium on **Diabetes, Hypertension, Metabolic Syndrome & Pregnancy**
Mar 8 - 12, 2017
Spain / Barcelona
Contact: Comtecmed
Phone: 011-972-3-566-6166
Email: info@comtecmed.com

2017 Advanced **Prostate Cancer** Consensus Conference
Mar 9 - 11, 2017
Switzerland / St. Gallen
Contact: Conference Secretariat, Kantonsspital St.Gallen Department of Oncology & Haematology
Phone: 011-41-71-494-1099
Email: prostatecancerconsensus@kssg.ch

2017 International Society for **Dermatologic Surgery** (ISDS) Expert Spring meeting with anatomy preparation course
Mar 9 - 10, 2017
Austria / Graz
Contact: ISDS Congress Office
Phone: 011-49-6151-951-8892
Fax: 011-49-6151-951-8893
Email: info@isdsworld.com

4th International Congress on Controversies in **Rheumatology & Autoimmunity** (CORA)
Mar 9 - 11, 2017
Italy / Bologna
Contact: CORA Secretariat, Kenes Group
Phone: 011-41-22-908-0488
Email: cora@kenes.com

Transanal Total **Mesorectal Excision** Course
Mar 9, 2017
Canada / Ontario / Toronto
Contact: Continuing Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719
Email: info-sur1621@cpdtoronto.ca

2017 Chellaram Diabetes Institute (CDI) International **Diabetes** Summit
Mar 10 - 12, 2017
India / Pune
Contact: Ms Nandini Ganatra, Secretariat, Chellaram Diabetes Institute
Phone: 091-20-6683-9767
Fax: 091-20-6683-9701
Email: ids@cdi.org.in

2017 **Musculoskeletal MR & Ultrasound Imaging** Course
Mar 11 - 14, 2017
Canada / British Columbia / Whistler
Contact: Sean Murphy, Department of Radiology, University of British Columbia
Phone: 604-875-4111 Ext. 20589
Email: Sean.murphy2@vch.ca

2017 Society for **Cardiothoracic Surgery** in Great Britain & Ireland (SCTS) Annual Meeting & Cardiothoracic Forum
Mar 12 - 14, 2017
United Kingdom / Belfast
Contact: Isabelle Ferner, Organizer, SCTS
Phone: 011-44-20-7869-6893
Email: sctsadmin@scts.org

2017 Snowmass **Retina & Eye**
Mar 13 - 17, 2017
United States / Colorado / Snowmass
Contact: Physician's Conferences Association & Eye Research Foundation
Phone: 772-287-1750
Fax: 772-287-0507

2nd Annual **Genetics in Forensics** Congress
Mar 14 - 15, 2017
United Kingdom / London
Contact: Guillaume Alonso, Oxford Global
Email: g.alonso@oxfordglobal.co.uk

British Institute of Radiology (BIR) / DMC Imaging Hands-on Training Series: **MRI of the Knee**
Mar 14, 2017
United Kingdom / London
Contact: Bir
Phone: 011-44-20-3668-2220
Fax: 011-44-20-3411-6354
Email: conference@bir.org.uk

11th World **Immune Regulation** Meeting (WIRM)
Mar 15 - 18, 2017
Switzerland / Davos
Contact: Ms. Sandra Crameri, Wirm Assistant, Swiss Institute of Allergy And Asthma Research
Phone: 011-41-81-410-0842
Fax: 011-41-81-410-0840

2017 St. Gallen International **Breast Cancer** Conference
Mar 15 - 18, 2017
Austria / Vienna
Contact: St. Gallen Oncology Conferences
Phone: 011-41-71-243-0032
Fax: 011-41-71-245-6805
Email: info@oncoconferences.ch

2017 International Congress on Clinical Trials in **Oncology & Hemato-Oncology**
Mar 16 - 17, 2017
United Kingdom / London
Contact: Debi Bert, Assistant Project Manager, Bio Events
Email: info@bioevents.net

4th Latin America Congress on Controversies to Consensus in **Diabetes, Obesity & Hypertension**
Mar 16 - 18, 2017
Argentina / Buenos Aires
Contact: Organizer, Comtecmed
Email: codhyla@codhy.com

Pet 3: Paediatric Epilepsy training
Mar 16 - 17, 2017
United Kingdom / Bristol
Contact: Leanne Broadley, Short Course Co-Ordinator, British Paediatric Neurology Association
Phone: 011-44-12-0452-6002
Email: leanne.broadley@bpna.org.uk

12th Congress of Asia & Oceania **Thyroid** Association
Mar 16 - 19, 2017
South Korea / Busan
Contact: Lucy Choi, Secretariat, MCI Korea
Phone: 011-82-708-766-9568
Fax: 011-82-2-576-9945
Email: office@aota2017.com

2017 International congress on clinical trials in **Oncology & Hemato-Oncology**
Mar 16 - 17, 2017
United Kingdom / London
Contact: Debi Bert, Assistant Project Manager, Bio Events
Email: info@bioevents.net

21st Annual Mcgill University CME update in **Otolaryngology: Head & Neck Surgery**
Mar 17 - 19, 2017
Canada / Quebec / Mont Tremblant
Contact: Mrs. Rosa Gasparrini, Department of Otolaryngology-Head and Neck Surgery, Mcgill University Health Centre
Phone: 514-934-1934 Ext. 34974
Email: rosa.gasparrini@muhc.mcgill.ca

Pet 1: Paediatric Epilepsy training
Mar 17, 2017
United Kingdom / Peterborough, UK
Contact: Leanne Broadley, Short Course Co-Ordinator, British Paediatric Neurology Association
Phone: 011-44-12-0452-6002
Email: leanne.broadley@bpna.org.uk

45th Annual Society for **Clinical Vascular Surgery** (SCVS) Symposium
Mar 18 - 22, 2017
United States / Florida / Lake Buena Vista
Contact: SCVS
Phone: 978-927-8330; Fax: 978-524-0498

2017 **Nephrology**
Mar 19 - 24, 2017
United States / Massachusetts / Boston
Contact: HMS-DCE, Nephrology 2017 Program Coordinator, Harvard Medical School
Phone: 617-384-8600
Email: ceprograms@hms.harvard.edu

Molecular Helminthology: An integrated approach
Mar 19 - 22, 2017
United States / Massachusetts / Cape Cod
Contact: Elsevier Conferences
Email: c.mole@elsevier.com

2017 **Adolescent Forensic Psychiatry** Sig Conference
Mar 20, 2017
United Kingdom / London
Contact: Louise Harman, Royal College of Psychiatrists
Phone: 011-44-20-3701-2630
Fax: 011-44-20-3701-2761
Email: louise.harman@rcpsych.ac.uk

2017 Royal College of **Obstetricians & Gynaecologists** World Congress
Mar 20 - 22, 2017
South Africa / Cape Town
Contact: Gill Slaughter, General Enquiries, Turners Conferences and Conventions Pty Ltd
Phone: 011-27-31-368-8000
Email: gills@turnergroup.co.za

2017 Society for **Endocrinology** (SFE) clinical update
Mar 20 – 22, 2017
United Kingdom / Birmingham
Contact: Conferences and Events, SFE
Phone: 011-44-14-5464-2210; Fax: 011-44-14-5464-2222
Email: conferences@endocrinology.org

3rd International **Hidden Hunger** congress
Mar 20 - 22, 2017
Germany / Stuttgart
Contact: Jana Tinz, M.Sc., Universitat Hohenheim / Institute of Biological Chemistry and Nutrition
Phone: 011-49-711-4592-2291
Email: hiddenhunger@uni-hohenheim.de

Infectious Diseases: Adult issues in the outpatient & inpatient settings
Mar 20 - 24, 2017
United States / Florida / Sarasota
Contact: Tara Esteves, Live Cme Manager, American Medical Seminars, Inc.
Phone: 866-267-4263 (Toll Free) Or 941-388-1766; Fax: 941-365-7073
Email: testeves@ams4cme.com

Specialty Skills in **Breast Surgery:** Principles in breast reconstruction **(Level 1)**
Mar 20 – 21, 2017
United Kingdom / London
Contact: Education, Royal College Of Surgeons Of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

3rd International Congress on **Medical Writing**
Mar 21 – 23, 2017
Egypt / Cairo
Contact: Mohamed Magdy, Pure Spot
Email: info@egypure.org

6th Annual Middle East Congress on **Clinical Nutrition**
Mar 21 - 23, 2017
Egypt / Cairo
Contact: Cairo Office, Pure Spot Congress & Event Organizers
Phone: 011-20-2-2672-1944
Fax: 011-20-2-2671-8421
Email: info@nutrition-me.org

Specialty Skills in **Coloproctology**
Mar 22, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

2017 Society of American **Gastrointestinal & Endoscopic Surgeons** (SAGES) annual meeting
Mar 22 - 25, 2017
Texas / Houston
Contact: Sages
Phone: 310-437-0555

2017 South African Society of **Anaesthesiologists** (SASA) Congress
Mar 22 - 26, 2017
South Africa / Johannesburg
Contact: Congress Management, Eastern Sun Events
Phone: 011-27-41-374-5654
Email: Sasa2017@Easternsun.Co.Za

How to Write A Surgical Paper
Mar 22, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: Education@Rcseng.Ac.Uk

Specialty skills in **Coloproctology**
Mar 22, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: Education@Rcseng.Ac.Uk

2017 **Brain Skin** Colloquium
Mar 23 - 24, 2017
United Kingdom / Manchester
Contact: British Association of Dermatologists
Email: conference@bad.org.uk

2017 World congress on **Osteoporosis, Osteoarthritis & Musculoskeletal Diseases**
Mar 23-26, 2017
Italy / Florence
Contact: Sophie Leisten, Congress Secretariat, Humacom
Phone: 011-32-87-852-652
Email: info@humacom.com

25th Annual Asian Society for **Cardiovascular & Thoracic Surgery** (ASCVTS) meeting
Mar 23 - 26, 2017
South Korea / Seoul
Contact: Ascvts Secretariat, Insession International Convention Services, Inc.
Phone: 011-82-2-6207-8177 or 011-82-2-3471-8555
Fax: 011-82-2-521-8683
Email: reg@ascvts2017.org

5th International congress on **Dual Disorders**
Mar 23 - 26, 2017
Spain / Madrid
Contact: Alejandro Hernandez, Kenes Group
Phone: 011-972-3-972-7450
Email: secretariat@icdd-congress.com

Menopause Special Skills module
Mar 23 - 24, 2017
United Kingdom / Kenilworth
Contact: Kate Ellis, British Menopause Society
Phone: 011-44-16-2889-0199
Email: kate.ellis@bms-whc.org.uk

4th Australia & New Zealand Academy for **Eating Disorders** (ANZAED) Autumn workshop series
Mar 24 - 25, 2017
Australia / Noosa
Contact: Anzaed
Phone: 011-61-2-8007-6875 or 011-64-9-887-0552
Email: anzaed@anzaed.org.au

Palliative Radiotherapy
Mar 24, 2017
United Kingdom / London
Contact: British Institute of Radiology
Phone: 011-44-20-3668-2220
Fax: 011-44-20-3411-6354
Email: conference@bir.org.uk

2017 **Pain** Association of Singapore (PAS) Annual Scientific Meeting
Mar 25, 2017
Singapore / Singapore
Contact: Pas Secretariat, Pas
Phone: 011-65-6513-7310
Email: pas@globewerks.com

Thyroid & Parathyroid Masterclass
Mar 27, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

13th International Conference on **Alzheimer's & Parkinson's** diseases
Mar 29 - Apr 2, 2017
Austria / Vienna
Contact: Ad/Pd Secretariat, Kenes International
Phone: 011-41-2-2908-0488
Email: adpd@kenes.com

9th Annual Bit International Congress of **Antibodies**
Mar 29 - 31, 2017
China / Beijing
Contact: Ms. Jessie Li, Manager, Bit
Phone: 011-86-411-8479-9609 Ext. 842
Fax: 011-86-411-8479-9629
Email: jessie@bit-ica.com

Principles of **Medical Education**: Maximizing Your Teaching Skills
Mar 29 - 31, 2017
United States / Massachusetts / Boston
Contact: Harvard Medical School Department of Continuing Education
Phone: 617-384-8600
Email: ceprograms@hms.harvard.edu

11th Congress of **General Practice**
Mar 30 - Apr 1, 2017
France / Paris
Contact: Overcome
Phone: 011-33-1-4088-9797
Email: cmgf@overcome.fr

14th Global Experts Meeting on **Nanomaterials & Nanotechnology**
Mar 30 - 31, 2017
Spain / Madrid
Contact: Richard Limner, Conference Series Llc
Phone: 888-843-8169; Fax: +1-650-618-1417
Email: nanomaterials@conferenceseries.com

19th British **Maternal & Fetal Medicine** Society (BMFMS) annual conference
Mar 30 - 31, 2017
Netherlands / Amsterdam
Contact: Administrator, BMFMS
Email: bmfms@rcog.org.uk

2017 American Academy of **Clinical Psychiatrists** / Current Psychiatry update
Mar 30 - Apr 1, 2017
United States / Illinois / Chicago
Contact: Jennifer Meade, Global Academy for Medical Education
Phone: 973-290-8258
Email: j.meade@globalacademycme.com

4th World congress on C**ontroversies in Pediatrics** (COPEDIA)
Mar 30 - Apr 1, 2017
Netherlands / Amsterdam
Contact: Secretariat, Secretariat, Congressmed
Phone: 011-41-22-339-9985
Email: copedia@congressmed.com

8th World congress on controversies in **Ophthalmology**
Mar 30 - Apr 1, 2017
Spain / Madrid
Contact: Natalie Ross, Congress Secretariat, Comtecmed
Phone: 011-972-3-566-6166
Fax: 011-972-3-566-6177
Email: cophy@comtecmed.com

Advanced **Upper Extremity Trauma** course (With Human Anatomical Specimens)
Mar 30 - Apr 1, 2017
United States / Florida / Miami
Contact: Ao North America
Phone: 800-769-1391 or 610-695-2459
Fax: 610-695-2420
Email: customerservice@aona.org

Basic **Surgical Anatomy** of the Head & Neck
Mar 30 - 31, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

5th International congress on **Dual Disorders & Dual Psycho-Pathology**
Mar 30 - Apr 2, 2017
Spain / Madrid
Contact: Alejandro Hernandez, Congress Secretariat, Kenes Group
Phone: 011-972-3-972-7450
Email: mediatks@kenes.com

2017 **Sexual Health** Conference
Mar 31 - Apr 1, 2017
Canada / British Columbia / Vancouver
Contact: Continuing Professional Development, University of British Columbia
Phone: 604-875-5101; Fax: 604-875-5078
Email: cpd.info@ubc.ca

Child Psychotherapy
Mar 31 - Apr 1, 2017
United States / Massachusetts / Boston
Contact: Department of Global & Continuing Education, Harvard Medical School
Phone: 617-384-8600
Email: Ceprograms@Hms.Harvard.Edu

CME on the run! 2016-2017 - **Gynecology & Urology**
Mar 31, 2017
Canada / British Columbia / Vancouver
Contact: Conference Registration, University Of British Columbia CPD
Phone: 604-875-5101; Fax: 604-875-5078
Email: cpd.info@ubc.ca

21st Annual Virginia Liver Symposium & Update in **Gastroenterology**
Apr 1, 2017
United States / Virginia / Richmond
Contact: Sage Blaska, Virginia Commonwealth University
Phone: 804-828-5415
Email: sage.blaska@vcuhealth.org

25th European Congress of **Psychiatry**
Apr 1 - 4, 2017
Italy / Florence
Contact: Congress Secretariat, European Psychiatric Association
Phone: 011-41-22-908-0488
Email: epa@kenes.com

28th International Symposium on **Cerebral Blood Flow, Metabolism & Function** / 13th International Conference on Quantification of Brain Function with Pet
Apr 1 - 4, 2017
Germany / Berlin
Contact: MCI Deutschland Gmbh
Phone: 011-49-30-204-590; Fax: 011-49-30-204-5950
Email: brain2017@mci-group.com

2nd International **Ayurveda** Congress
Apr 1 - 2, 2017
United Kingdom / London
Contact: M. Rickinger, International Maharishi Ayurveda Foundation
Phone: 011-31-4-7553-9546
Email: info@imavf.org

New treatments in **Chronic Liver Disease**
Apr 1 - 2, 2017
United States / California / San Diego
Contact: Scripps Conference Services & CME
Phone: 858-652-5400
Email: med.edu@scrippshealth.org

2017 British Society for **Parasitology** (BSP) Spring meeting
Apr 2 - 5, 2017
United Kingdom / Dundee
Contact: Bsp
Phone: 011-44-12-3421-1015; Fax: 011-44-12-3448-1015
Email: info@bsp.uk.net

15th World Congress on **Public Health**
Apr 3 – 7, 2017
Australia / Melbourne
Contact: MCI Australia
Phone: 011-61-3-9320-8600
Email: info@populationhealthcongress.org.au

2017 Association for **Molecular Pathology** Global Congress on Molecular Pathology
Apr 3 – 5, 2017
Germany / Berlin
Contact: MCI Deutschland Gmbh
Phone: 011-49-30-20-4590; Fax: 011-49-30-204-5950
Email: amp-berlin@mci-group.com

2017 British Society for **Investigative Dermatology** Annual Meeting
Apr 3 - 5, 2017
United Kingdom / Manchester
Contact: British Association of Dermatologists
Email: conference@bad.org.uk

34th British Society for **Dermatological Surgery** (BSDS) Annual Surgery workshop
Apr 3 - 5, 2017
United Kingdom / Newcastle
Contact: Bsds
Email: info@bsds.org.uk

Bone Research Society (BRS) training course: **Osteoporosis** & other Metabolic Bone Diseases
Apr 3 - 5, 2017
United Kingdom / Oxford
Contact: Janet Crompton, Course Organizer, BRS
Phone: 011-44-14-5354-9929
Email: events@boneresearchsociety.org

2017 Mayo Clinic **Extracorporeal Membrane Oxygenation** workshop
Apr 4 - 5, 2017
United States / Arizona / Scottsdale
Contact: Mayo School Of CPD, Mayo Clinic
Phone: 480-301-4580
Email: mca.cme@mayo.edu

2017 World Congress for **Cervical Pathology & Colposcopy**
Apr 4 - 7, 2017
United States / Florida / Orlando
Contact: American Society for Colposcopy & Cervical Pathology
Phone: 800-787-7227
Email: education@asccp.org

Advanced Skills in **Breast disease management**
Apr 4 - 7, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Operative Skills in **Urology**: Modules 3 & 4
Apr 4 - 5, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

57th Annual Update in **General Surgery**
Apr 5 - 8, 2017
Canada / Ontario / Toronto
Contact: Continuing Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719
Email: info-sur1704@cpdtoronto.ca

Practical Advances in **Musculoskeletal & Sports Care** Live Course
Apr 5 - 8, 2017
United States / Nevada / Las Vegas
Contact: American Academy of Family Physicians
Phone: 800-274-2237 or 913-906-6000; Fax: 913-906-6075

11th Annual **Risk & Recovery** Forensic Conference
Apr 6 - 7, 2017
Canada / Ontario / Hamilton
Contact: Josie Cosco, Forensic Psychiatry Program, St. Joseph's Healthcare Hamilton
Phone: 905-522-1155 Ext. 35415
Email: jcosco@stjoes.ca

13th Emirates **Critical Care** Conference
Apr 6 - 8, 2017
United Arab Emirates / Dubai
Contact: Anala Jamir, Project Manager, Infoplus Events Llc
Phone: 011-971-4-421-8996; Fax: 011-971-4-421-8838
Email: eccc@infoplusevents.com

2017 Multidisciplinary Update in **Pulmonary & Critical Care Medicine**
Apr 6 - 9, 2017
United States / Arizona / Phoenix
Contact: Mayo School of CPD, Mayo Clinic
Phone: 480-301-4580
Fax: 480-301-4580
Email: mca.cme@mayo.edu

Operative Skills in **Ear, Nose & Throat Surgery**
Apr 6 - 7, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

2017 **Immune Profiling** World Congress USA
Apr 10 - 12, 2017
United States / District of Columbia / Washington
Contact: Ina Luft, Terrapinn
Phone: 011-44-20-7092-1191
Email: ina.luft@terrapinn.com

Influenza & Respiratory Vaccine Conference
Apr 10 - 12, 2017
United States / District of Columbia / Washington
Contact: Ina Luft, Terrapinn
Phone: 011-44-20-7092-1191
Email: ina.luft@terrapinn.com

6th Global Experts Meeting on **Cardiovascular Pharmacology** & Cardiac Medications
Apr 13 - 14, 2017
United Arab Emirates / Dubai
Contact: Alisa Craig, Program Manager, Conference Series Llc
Phone: 702-508-5200
Email: cardiacpharmacology@conferenceseries.net

12th International Society of **Dermatology (ISD)** International Congress of Dermatology
Apr 18 - 22, 2017
Argentina / Buenos Aires
Contact: Cindy Froehlich, Executive Director, ISD
Phone: 386-437-4405
Email: info@intsocderm.org

18th World Congress of the World Association for **Dynamic Psychiatry**
Apr 19 – 22, 2017
Italy / Florence
Contact: Secretariat, Net Congress & Education
Phone: 011-39-2-9143-4000; Fax: 011-39-2-9143-4059
Email: segreteria@netcongresseducation.com

2017 **Influenza Vaccines** for the World
Apr 19 - 21, 2017
Switzerland / Lausanne
Contact: John Herriot, Planning Director, Meetings management
Phone: 011-44-14-8342-7770
Fax: 011-44-14-8342-8516
Email: jherriot@meetingsmgmt.u-net.com

2017 International **Liver Congress**
Apr 19 - 23, 2017
Netherlands / Amsterdam
Contact: Congress Organizer, European Association for the Study of the Liver
Phone: 011-41-2-2807-0360
Email: com@easloffice.eu

18th Annual National Conference on **Fetal Monitoring**
Apr 20 - 22, 2017
United States / Nevada / Las Vegas
Contact: Symposia Medicus
Phone: 800-327-3161
Fax: 925-969-1795

42nd Annual Meeting of the Society for **Sex Therapy & Research** (SSTAR)
Apr 20 - 23, 2017
Canada / Quebec / Montreal
Contact: Sstar
Phone: 847-647-8832
Email: info@sstarnet.org

4th Singapore-Australian & New Zealand **Intensive Care** Society Intensive Care Forum
Apr 20 - 24, 2017
Singapore / Singapore
Contact: Francisca Ang Wei Hoon, Kenes Asia
Phone: 011-65-6389-6616
Email: fang@kenes.com

5th Emirates International **Orthopaedic Congress**
Apr 20 - 22, 2017
United Arab Emirates / Dubai
Contact: Epin Kurra, Project Manager, Infoplus Events
Phone: 011-971-4-421-8996
Fax: 011-971-4-421-8838
Email: ortho@infoplusevents.com

6th World Congress on **ADHD**
Apr 20 - 23, 2017
Canada / British Columbia / Vancouver
Contact: Congress Organizer, CPO Hanser Service
Email: adhd2017@cpo-hanser.de

Urological Anatomy for Surgery
Apr 21, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

25th Annual International Society for **Magnetic Resonance in Medicine** (ISMRM) Meeting & Exhibition
Apr 22 - 27, 2017
United States / Hawaii / Honolulu
Contact: Melisa Martinez, Meetings Coordinator, ISMRM
Phone: 510-841-1899
Fax: 510-841-2340
Email: melisa@ismrm.org

27th European Congress of **Clinical Microbiology & Infectious Diseases**
Apr 22 - 25, 2017
Austria / Vienna
Contact: Conference Secretariat, European Society Of Clinical Microbiology & Infectious Diseases
Phone: 011-41-61-508-0172
Email: eccmidinfo@escmid.org

Non-Small Cell Lung Cancer Hands-On Summit
Apr 22, 2017
United States / Missouri / St. Louis
Contact: American College Of Chest Physicians
Phone: 800-343-2227 (Us Only) Or 224-521-9800; Fax: 224-521-9801

102nd American **Occupational Health** Conference
Apr 23 - 26, 2017
United States / Colorado / Denver
Contact: American College of Occupational & Environmental Medicine
Phone: 847-818-1800; Fax: 847-818-9266

1st World Congress on **Maternal Fetal Neonatal Medicine**
Apr 23 - 26, 2017
United Kingdom / London
Contact: Congress Organizer, MCA Scientific Events
Phone: 011-39-2-3493-4404
Email: info@worldmfnm.eu

85th European **Atherosclerosis** Society Congress
Apr 23 - 26, 2017
Czech Republic / Prague
Contact: Congress Secretariat, Aim Group International - Milan Office
Phone: 011-39-2-56-6011; Fax: 011-39-2-5660-9045
Email: eas2017@aimgroup.eu

Radiology in Venice
Apr 23 – 29, 2017
Italy / Venice
Contact: Denise Mora, Radiology International, Inc.
Phone: 800-481-1873 (Us) Or 860-225-1700
Email: denise@radiologyintl.com

10th Annual **Antibodies & Proteins** Congress
Apr 24 - 25, 2017
United Kingdom / London
Contact: Danielle Dalby, Senior Marketing Manager, Oxford Global
Phone: 011-44-18-6524-8455; Fax: 011-44-18-6525-0985
Email: d.dalby@oxfordglobal.co.uk

4th Annual **Peptides** Congress
Apr 24 - 25, 2017
United Kingdom / London
Contact: Guilaume Alonso, Marketing Executive, Oxford Global
Phone: 011-44-18-6524-8455
Email: g.alonso@oxfordglobal.co.uk

Advanced Educational Courses in **Plastic Surgery: Head & Neck, Facial Palsy**
Apr 24 - 25, 2017
United Kingdom / Manchester
Contact: Secretariat, British Association of Plastic Reconstructive & Aesthetic Surgeons
Phone: 011-44-20-7831-5161
Email: secretariat@bapras.org.uk

Cardiothoracic & Body Imaging
Apr 24 - 27, 2017
United States / California / Rancho Mirage
Contact: Lori Ehrich, Manager, Radiology CME, Penn Medicine/Department of Radiology
Phone: 215-662-6904; Fax: 215-349-5925
Email: cme@rad.upenn.edu

Operative Skills in **Neurosurgery**
Apr 24 - 26, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: Education@Rcseng.Ac.UK

2017 World Association for **Disaster & Emergency Medicine** (WADEM) Congress on Disaster & Emergency Medicine
Apr 25 - 28, 2017
Canada / Ontario / Toronto
Contact: Wadem
Phone: 608-819-6604
Fax: 608-819-6055
Email: info@wadem.org

Intermediate Skills in **Laparoscopic Surgery**
Apr 25 - 26, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Update on **Chronic Kidney Disease**
Apr 25, 2017
United States / Pennsylvania / Hershey
Contact: Department of Continuing Education, Pennsylvania State University
Phone: 717-531-6483
Fax: 717-531-5604
Email: continuinged@hmc.psu.edu

2017 British **Renal Society** (BRS) Conference
Apr 26 - 28, 2017
United Kingdom / Nottingham
Contact: British Renal Society
Phone: 011-44-15-4344-2153
Fax: 011-44-12-1355-2420
Email: brs@britishrenal.org

2017 Combined **Otolaryngology** Spring Meetings
Apr 26 - 30, 2017
United States / California / San Diego
Contact: Marisa Villalba, Meeting or Hotel Inquiries
Phone: 312-202-5322
Email: mvillalba@facs.org

76th Annual Society for **Investigative Dermatology** (SID) Meeting
Apr 26 - 29, 2017
United States / Oregon / Portland
Contact: Sid
Phone: 216-579-9300; Fax: 216-579-9333
Email: sid@sidnet.org

Challenges in **Male & Female Sexual Healthcare**
Apr 26 - 29, 2017
United States / Florida / St. Petersburg
Contact: Symposia Medicus
Phone: 800-327-3161; Fax: 925-969-1795

15th International **Integrative Oncology** Conference
Apr 27 - 29, 2017
United States / California / San Diego
Contact: Debbie Curtis, Administrator, Best answer for Cancer Foundation
Phone: 512-342-8181
Email: admin@bestanswerforcancer.org

2017 American Association of **Genitourinary Surgeons** (AAGUS) annual meeting
Apr 27 - 30, 2017
United States / Florida / Key Biscayne
Contact: Jeannette Sofia
Phone: 708-216-5100; Fax: 708-216-8991
Email: aagusorg@yahoo.com

Speciality Skills in **Emergency Surgery & Trauma**
Apr 27 - 28, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

2017 American Congress of **Rehabilitation Medicine** (ACRM) Mid-Year Meeting
Apr 28 - 29, 2017
United States / Georgia / Atlanta
Contact: Acrm
Phone: 703-435-5335; Fax: 866-692-1619
Email: info@acrm.org

4th Annual Clinical Advances in **Arrhythmias & Cardiovascular Disease**
Apr 28 - 30, 2017
United States / California / San Diego
Contact: Scripps Conference Services & Cme
Phone: 858-652-5400
Email: med.edu@scrippshealth.org

CME on the Run! 2016-2017 - **Palliative Care & Geriatrics**
Apr 28, 2017
Canada / British Columbia / Vancouver
Contact: Conference Registration, Ubc Cpd
Phone: 604-875-5101; Fax: 604-875-5078
Email: cpd.info@ubc.ca

Human Body in Motion (HBIM) International Congress: From Lab to Practice - How to close the gap between research & patients?
Apr 28 - 29, 2017
Belgium / Brussels
Contact: Van Hove Olivier, HBIM
Phone: 011-32-2-555-6489
Email: olivier.van.hove@ersame.ulb.ac.be

What every hand surgeon should know about the wrist: **Distal Radius, Carpus & Ulnar-Sided Wrist Pain**
Apr 28 - 29, 2017
United States / Colorado / Denver
Contact: American Society for Surgery of the Hand
Phone: 312-880-1900
Email: info@assh.org

Evidence Based **Assistive Reproductive Technology**: 1st International Symposium
Apr 29 - 30, 2017
Turkey / Antalya
Contact: Merih Altun, Mrs., Gelecek the Center for Human Reproduction
Phone: 011-90-24-2324-2526
Email: tbmd2016@gmail.com

11th International Society of **Physical & Rehabilitation Medicine** Congress
Apr 30 - May 4, 2017
Argentina / Buenos Aires
Contact: Secretariat, Kenes International
Phone: 011-41-22-908-0488
Email: isprm@kenes.com

6th World **Intracranial Hemorrhage** & Heads Conference
May 1 - 3, 2017
United States / Maryland / Baltimore
Contact: Kenes Group, Congress Secretariat, Kenes Group
Phone: 011-90-53-4517-2181
Email: atoraman@kenes.com

Intermediate Skills in **Plastic Surgery**: Facial Soft Tissue Reconstruction
May 2 - 3, 2017
United Kingdom / London
Contact: Education, Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

2017 **Myelodysplastic Syndromes** Symposium
May 3 - 6, 2017
Spain / Valencia Oncology
Contact: Ron Marcovici, Kenes Group
Phone: 011-41-22-908-0488
Email: rmarcovici@kenes.com

19th Annual International Society for **Bipolar Disorders** Conference
May 4 - 7, 2017
United States / Washington
Contact: Ron Marcovici, Kenes Group
Phone: 011-41-22-908-0488

WHO-Facts Sheet

1. Microcephaly
2. Lymphatic Filariasis
3. Guillain–Barré Syndrome
4. Violence Against Women
5. Cardiovascular Diseases (CVDs)
6. Dioxins and Their Effects on Human Health

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2016; 48 (4) : 374 - 386

1. MICROCEPHALY

Overview

Microcephaly is a condition where a baby has a head size much smaller compared to other babies of the same age and sex. Head size is an important measurement to monitor a child's brain growth. The severity of microcephaly ranges from mild to severe. Microcephaly can be present at birth (congenital) or may develop postnatally (acquired).

KEY FACTS

- Microcephaly is a condition where a baby is born with a small head or the head stops growing after birth.
- Microcephaly is a rare condition. One baby in several thousand is born with microcephaly.
- The most reliable way to assess whether a baby has microcephaly is to measure head circumference 24 hours after birth, compare the value with WHO growth standards, and continue to measure the rate of head growth in early infancy.
- Babies born with microcephaly may develop convulsions and suffer physical and learning disabilities as they grow older.
- There are no specific tests to determine, if a baby will be born with microcephaly, but ultrasound scans in the third trimester of pregnancy can sometimes identify the problem.
- There is no specific treatment for microcephaly.

Scope of the problem

Microcephaly is a rare condition. Reported estimate incidence of microcephaly has wide variation due to the differences in the definition and target population.

Increased number or clustering of cases of microcephaly have been reported in context of outbreaks of Zika virus infection. The most likely explanation of available evidence is that Zika virus infection during pregnancy is a cause of congenital brain abnormalities including microcephaly.

In addition to microcephaly, a range of manifestations of varying severity has been reported among newborns that were exposed to Zika virus in utero. These include malformations of the head, seizures, swallowing problems, hearing and sight abnormalities. Other outcomes associated with Zika virus infection in utero may involve miscarriages and stillbirths. Together, this spectrum is referred to as 'congenital Zika virus syndrome.'

Diagnosis

Early diagnosis of microcephaly can sometimes be made by fetal ultrasound. Ultrasounds have the best diagnosis possibility, if they are made at the end of the second trimester, around 28 weeks, or in the third trimester of pregnancy. Often diagnosis is made at birth or at a later stage.

Babies should have their head circumference measured in the first 24 hours after birth and compared with WHO growth standards. The result will be interpreted in relation to the gestational age of the baby, and also the baby's weight and length. Suspected cases should be reviewed by a paediatrician, have brain imaging scans, and have their head circumference measured at monthly intervals in early infancy and compared with growth standards. Doctors should also test for known causes of microcephaly.

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Causes of microcephaly

There are many potential causes of microcephaly, but often the cause remains unknown. The most common causes include:

- infections during pregnancy: toxoplasmosis (caused by a parasite found in undercooked meat), Campylobacter pylori, rubella, herpes, syphilis, cytomegalovirus, HIV and Zika;
- exposure to toxic chemicals: maternal exposure to heavy metals like arsenic and mercury, alcohol, radiation, and smoking;
- pre- and perinatal injuries to the developing brain (hypoxia-ischemia, trauma);
- genetic abnormalities such as Down syndrome; and
- severe malnutrition during fetal life.

Based on a systematic review of the literature up to 30 May 2016, WHO has concluded that Zika virus infection during pregnancy is a cause of congenital brain abnormalities, including microcephaly; and that Zika virus is a trigger of Guillain-Barré syndrome.

Signs and symptoms

Many babies born with microcephaly may demonstrate no other symptoms at birth, but go on to develop epilepsy, cerebral palsy, learning disabilities, hearing loss and vision problems. In some cases, children with microcephaly develop entirely normally.

Treatment and care

There is no specific treatment for microcephaly. A multidisciplinary team is important to assess and care for babies and children with microcephaly. Early intervention with stimulation and play programs may show positive impacts on development. Family counseling and support for parents is also extremely important.

WHO response

WHO has been working closely with countries affected by Zika virus and related complications on the investigation of and response to the outbreak since mid-2015.

The Strategic Response Framework and Joint Operations Plan outlines steps that WHO is taking with partners to respond to Zika and potential complications.

- Working closely with affected countries on the Zika outbreak investigation and response and on the unusual increase in microcephaly cases.
- Engaging communities to communicate the risks associated with Zika virus disease and how they can protect themselves.
- Providing guidance and mitigating the potential impact on women of childbearing age and those who are pregnant, as well as families affected by Zika virus.
- Helping affected countries strengthen care for pregnant women and the families of children born with microcephaly.
- Investigating the reported increase in microcephaly cases and the possible association with Zika virus infection by bringing together experts and partners.
- Describing the full spectrum of congenital Zika virus syndrome, which may evolve, as part of the WHO Zika virus research agenda.

2. LYMPHATIC FILARIASIS

Overview

Lymphatic filariasis, commonly known as elephantiasis, is a neglected tropical disease. Infection occurs when filarial parasites are transmitted to humans through mosquitoes. Infection is usually acquired in childhood causing hidden damage to the lymphatic system.

The painful and profoundly disfiguring visible manifestations of the disease, lymphoedema, elephantiasis and scrotal swelling occur later in life and lead to permanent disability. These patients are not only physically disabled, but suffer mental, social and financial losses contributing to stigma and poverty.

KEY FACTS

- Lymphatic filariasis can result in an altered lymphatic system and the abnormal enlargement of body parts, causing pain, severe disability and social stigma.
- Nine hundred forty-seven million people in 54 countries worldwide remain threatened by lymphatic filariasis and require preventive chemotherapy to stop the spread of this parasitic infection.
- In year 2000, over 120 million people were infected, with about 40 million disfigured and incapacitated by the disease.
- Lymphatic filariasis can be eliminated by stopping the spread of infection through preventive chemotherapy with single doses of two medicines for persons living in areas where the infection is present. 6.2 billion treatments have been delivered to stop the spread of infection since 2000.
- Three hundred fifty-one million people no longer require preventive chemotherapy due to successful implementation of WHO strategies.
- A basic, recommended package of care can alleviate suffering and prevent further disability among lymphatic filariasis patients.

The disease

Currently, 947 million people in 54 countries are living in areas that require preventive chemotherapy to stop the spread of infection. Approximately 80% of these people are living in the following 10 countries: Angola, Cameroon, Côte d'Ivoire , Democratic Republic of the Congo, India, Indonesia, Mozambique, Myanmar, Nigeria and the United Republic of Tanzania.

Globally, an estimated 25 million men suffer with genital disease and over 15 million people are afflicted with lymphoedema. Eliminating lymphatic filariasis can prevent unnecessary suffering and contribute to the reduction of poverty.

Cause and transmission

Lymphatic filariasis is caused by infection with parasites classified as nematodes (roundworms) of the family Filariodidea. There are three types of these thread-like filarial worms:

- *Wuchereria bancrofti*, which is responsible for 90% of the cases
- *Brugia malayi*, which causes most of the remainder of the cases
- *Brugia timori*, which also causes the disease.

Adult worms lodge in the lymphatic system and disrupt the immune system. The worms can live for an average of 6 - 8 years and, during their life time, produce millions of microfilariae (immature larvae) that circulate in the blood.

Mosquitoes are infected with microfilariae by ingesting blood when biting an infected host. Microfilariae mature into infective larvae within the mosquito. When infected mosquitoes bite people, mature parasite larvae are deposited on the skin from where they can enter the body. The larvae then migrate to the lymphatic vessels where they develop into adult worms, thus continuing a cycle of transmission.

Lymphatic filariasis is transmitted by different types of mosquitoes for example by the *Culex* mosquito, widespread across urban and semi-urban areas, Anopheles, mainly found in rural areas, and Aedes, mainly in endemic islands in the Pacific.

Symptoms

Lymphatic filariasis infection involves asymptomatic, acute, and chronic conditions. The majority of infections are asymptomatic, showing no external signs of infection. These asymptomatic infections still cause damage to the lymphatic system and the kidneys, and alter the body's immune system.

Acute episodes of local inflammation involving skin, lymph nodes and lymphatic vessels often accompany chronic lymphoedema or elephantiasis. Some of these episodes are caused by the body's immune response to the parasite. Most are the result of bacterial skin infection, however, where normal defences have been partially lost due to underlying lymphatic damage.

When lymphatic filariasis develops into chronic conditions, it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and hydrocele (scrotal swelling). Involvement of breasts and genital organs is common. Such body deformities lead to social stigma, as well as financial hardship from loss of income and increased medical expenses. The socioeconomic burdens of isolation and poverty are immense.

WHO's response

World Health Assembly resolution WHA50.29 encourages Member States to eliminate lymphatic filariasis as a public health problem. In response, WHO launched its Global Program to Eliminate Lymphatic Filariasis (GPELF) in 2000. In 2012, the WHO neglected tropical diseases roadmap reconfirmed the target date for achieving elimination by 2020.

WHO's strategy is based on 2 key components:

- stopping the spread of infection through large-scale annual treatment of all eligible people in an area or region where infection is present; and
- alleviating the suffering caused by lymphatic filariasis through increased morbidity management and disability prevention activities.

Large-scale treatment (preventive chemotherapy)

Elimination of lymphatic filariasis is possible by stopping the spread of the infection. Large-scale treatment involves a single dose of two medicines given annually to an entire at-risk population in the following way: albendazole (400 mg) together with either ivermectin (150 - 200 mcg/kg) or with diethylcarbamazine citrate (DEC) (6 mg/kg).

These medicines have a limited effect on adult parasites but effectively reduce the density of microfilariae in the bloodstream and prevent the spread of parasites to mosquitoes. This recommended large-scale treatment strategy is called preventive chemotherapy when conducted annually for 4 – 6 years, and it can interrupt the transmission cycle.

At the start of GPELF, 81 countries were considered endemic for lymphatic filariasis. Further epidemiological data indicated that preventive chemotherapy was not required in nine countries. From year 2000 to 2015, 6.2 billion treatments were delivered to more than 820 million people at least once in 64 countries, considerably reducing transmission in many places. Recent research data show that

the transmission of lymphatic filariasis in at-risk populations has dropped by 43% since the beginning of the GPELF. The overall economic benefit of the program during 2000 - 2007 is conservatively estimated at US$ 24 billion. The benefits of 14 years of MDA treatment is now estimated to avert US$ 100.5 billion over the lifetime of cohorts who have benefited from treatment.

Currently 73 countries are considered endemic for filariasis of which six of these (Cambodia, The Cook Islands, Maldives, Niue, Sri Lanka and Vanuatu) were acknowledged as achieving elimination of LF as a public health problem. Thirteen more countries have successfully implemented recommended strategies, stopped mass treatment and are under surveillance to demonstrate that elimination has been achieved.

Preventive chemotherapy is still required in 54 countries but has not been delivered to all endemic areas as of the end of 2015. Enhanced strategies are now required in about 29 countries to achieve elimination targets and stop treatment by year 2020.

Morbidity management

Morbidity management and disability prevention are vital for improving public health and should be fully integrated into the health system to ensure sustainability. Surgery can alleviate most cases of hydrocele. Clinical severity and progression of the disease, including acute inflammatory episodes, can be reduced and prevented with simple measures of hygiene, skin care, exercise, and elevation of affected limbs. People with lymphoedema must have access to continuing care throughout their lives, both to manage the disease and to prevent progression to more advanced stages.

The GPELF aims to provide access to a minimum package of care for every person with associated chronic manifestations of lymphatic filariasis in all areas where the disease is present, thus alleviating suffering and promoting improvement in their quality of life.

Success in 2020 will be achieved, if patients have access to the following minimum package of care:

- treatment for episodes of adenolymphangitis (ADL);
- guidance in applying simple measures to manage lymphoedema and hydrocele to prevent progression of lymphoedema and debilitating, inflammatory episodes of ADL;
- surgery for hydrocele;
- treatment with antifilarial medicines to destroy any remaining worms and microfilariae by preventive chemotherapy or individual treatment.

Vector control

Mosquito control is a supplemental strategy supported by WHO. It is used to reduce transmission of lymphatic filariasis and other mosquito-borne infections. Depending on the parasite-vector species, measures such as insecticide-treated nets, indoor residual spraying or personal protection measures may help protect people from infection. Vector control has in select settings contributed to the elimination of lymphatic filariasis in the absence of large-scale preventive chemotherapy.

3. GUILLAIN–BARRE SYNDROME

Overview

In Guillain-Barré syndrome, the body's immune system attacks part of the peripheral nervous system. The syndrome can affect the nerves that control muscle movement as well as those that transmit pain, temperature and touch sensations. This can result in muscle weakness and loss of sensation in the legs and/or arms.

It is a rare condition, and while it is more common in adults and in males, people of all ages can be affected.

KEY FACTS

- Guillain-Barré syndrome (GBS) is a rare condition in which a person's immune system attacks the peripheral nerves.
- People of all ages can be affected, but it is more common in adults and in males.
- Most people recover fully from even the most severe cases of Guillain-Barré syndrome.
- Severe cases of Guillain-Barré syndrome are rare, but can result in near-total paralysis.
- Guillain-Barré syndrome is potentially life-threatening. People with Guillain-Barré syndrome should be treated and monitored; some may need intensive care. Treatment includes supportive care and some immunological therapies.

Symptoms

Symptoms typically last a few weeks, with most individuals recovering without long-term, severe neurological complications.

- The first symptoms of Guillain-Barré syndrome include weakness or tingling sensations. They usually start in the legs, and can spread to the arms and face.
- For some people, these symptoms can lead to paralysis of the legs, arms, or muscles in the face. In 20 - 30% of people, the chest muscles are affected, making it hard to breathe.

- The ability to speak and swallow may become affected in severe cases of Guillain-Barré syndrome. These cases are considered life-threatening, and affected individuals should be treated in intensive-care units.
- Most people recover fully from even the most severe cases of Guillain-Barré syndrome, although some continue to experience weakness.
- Even in the best of settings, 3 - 5% of Guillain-Barré syndrome patients die from complications, which can include paralysis of the muscles that control breathing, blood infection, lung clots, or cardiac arrest.

Causes

Guillain-Barré syndrome is often preceded by an infection. This could be a bacterial or viral infection. Guillain-Barré syndrome may also be triggered by vaccine administration or surgery.

In the context of Zika virus infection, unexpected increase in cases of Guillain-Barré syndrome has been described in affected countries. The most likely explanation of available evidence from outbreaks of Zika virus infection and Guillain-Barré syndrome is that Zika virus infection is a trigger of Guillain-Barré syndrome.

Diagnosis

Diagnosis is based on symptoms and findings on neurological examination including diminished or loss of deep-tendon reflexes. A lumbar puncture may be done for supportive information, though it should not delay treatment. Other tests, such as blood tests, to identify the underlying trigger are not required to make the diagnosis of GBS and should not delay treatment.

Treatment and care

The following are recommendations for treatment and care of people with Guillain-Barré syndrome:

- Guillain-Barré syndrome is potentially life-threatening. GBS patients should be hospitalized so that they can be monitored closely.
- Supportive care includes monitoring of breathing, heartbeat and blood pressure. In cases where a patient's ability to breathe is impaired, he or she is usually put on a ventilator. All GBS patients should be monitored for complications, which can include abnormal heart beat, infections, blood clots, and high or low blood pressure.
- There is no known cure for GBS. But treatments can help improve symptoms of GBS and shorten its duration.
- Given the autoimmune nature of the disease, its acute phase is typically treated with immunotherapy, such as plasma exchange to remove antibodies from the blood or intravenous immunoglobulin. It is most often beneficial when initiated 7 to 14 days after symptoms appear.
- In cases where muscle weakness persists after the acute phase of the illness, patients may require rehabilitation services to strengthen their muscles and restore movement.

WHO Response

WHO is supporting countries to manage GBS in context of Zika virus infection by:

- Enhancing surveillance of GBS in Zika affected countries.
- Providing guidelines for the assessment and management of GBS.
- Supporting countries to implement guidelines and strengthen health systems to improve the management of GBS cases.
- Defining the research agenda for GBS.

4. VIOLENCE AGAINST WOMEN

Intimate Partner and Sexual Violence against Women

The United Nations defines violence against women as "any act of gender-based violence that results in, or is likely to result in, physical, sexual or mental harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or in private life."

KEY FACTS

- Violence against women – particularly intimate partner violence and sexual violence – are major public health problems and violations of women's human rights.
- Recent global prevalence figures indicate that about 1 in 3 (35%) of women worldwide have experienced either physical and/or sexual intimate partner violence or non-partner sexual violence in their lifetime.
- Most of this violence is intimate partner violence. Worldwide, almost one third (30%) of women who have been in a relationship report that they have experienced some form of physical and/or sexual violence by their intimate partner.
- Globally, as many as 38% of murders of women are committed by an intimate partner.
- Violence can negatively affect women's physical, mental, sexual and reproductive health, and may increase vulnerability to HIV.

- Factors associated with increased risk of perpetration of violence include low education, child maltreatment or exposure to violence in the family, harmful use of alcohol, attitudes accepting of violence and gender inequality.
- Factors associated with increased risk of experiencing intimate partner and sexual violence include low education, exposure to violence between parents, abuse during childhood, attitudes accepting violence and gender inequality.
- There is evidence from high-income settings that school-based programs may be effective in preventing relationship violence (or dating violence) among young people.
- In low-income settings, primary prevention strategies, such as microfinance combined with gender equality training and community-based initiatives that address gender inequality and relationship skills, hold promise.
- Situations of conflict, post conflict and displacement may exacerbate existing violence, such as by intimate partners, and present additional forms of violence against women.

Intimate partner violence refers to behavior by an intimate partner or ex-partner that causes physical, sexual or psychological harm, including physical aggression, sexual coercion, psychological abuse and controlling behaviors.

Sexual violence is "any sexual act, attempt to obtain a sexual act, or other act directed against a person's sexuality using coercion, by any person regardless of their relationship to the victim, in any setting. It includes rape, defined as the physically forced or otherwise coerced penetration of the vulva or anus with a penis, other body part or object."

Scope of the problem

Population-level surveys based on reports from victims provide the most accurate estimates of the prevalence of intimate partner violence and sexual violence in non-conflict settings. The first report of the "WHO Multi-country study on women's health and domestic violence against women" (2005) in 10 mainly low- and middle-income countries found that, among women aged 15 – 49:

- between 15% of women in Japan and 71% of women in Ethiopia reported physical and/or sexual violence by an intimate partner in their lifetime;
- between 0.3 – 11.5% of women reported sexual violence by someone other than a partner since the age of 15 years;
- the first sexual experience for many women was reported as forced – 17% of women in rural Tanzania, 24% in rural Peru, and 30% in rural Bangladesh reported that their first sexual experience was forced.

A more recent analysis of WHO with the London School of Hygiene and Tropical Medicine and the Medical Research Council, based on existing data from over 80 countries, found that globally, 35% of women have experienced either physical and/or sexual intimate partner violence or non-partner sexual violence. Most of this violence is intimate partner violence. Worldwide, almost one-third (30%) of all women who have been in a relationship have experienced physical and/or sexual violence by their intimate partner, in some regions this is much higher. Furthermore, globally as many as 38% of all murders of women are committed by intimate partners.

Intimate partner and sexual violence are mostly perpetrated by men against women. Child sexual abuse affects both boys and girls. International studies reveal that approximately 20% of women and 5 – 10% of men report being victims of sexual violence as children. Violence among young people, including dating violence, is also a major problem.

Risk factors

Factors associated with intimate partner and sexual violence occur at individual, family, community and wider society levels. Some factors are associated with being a perpetrator of violence, some are associated with experiencing violence and some are associated with both.

Risk factors for both intimate partner and sexual violence include:

- lower levels of education (perpetration of sexual violence and experience of sexual violence);
- exposure to child maltreatment (perpetration and experience);
- witnessing family violence (perpetration and experience);
- antisocial personality disorder (perpetration);
- harmful use of alcohol (perpetration and experience);
- having multiple partners or suspected by their partners of infidelity (perpetration); and
- attitudes that are accepting of violence and gender inequality (perpetration and experience).

Factors specifically associated with intimate partner violence include:

- past history of violence;
- marital discord and dissatisfaction;
- difficulties in communicating between partners.

Factors specifically associated with sexual violence perpetration include:
- beliefs in family honor and sexual purity
- ideologies of male sexual entitlement and
- weak legal sanctions for sexual violence.

The unequal position of women relative to men and the normative use of violence to resolve conflict are strongly associated with both intimate partner violence and non-partner sexual violence.

Health consequences

Intimate partner and sexual violence have serious short- and long-term physical, mental, sexual and reproductive health problems for survivors and for their children, and lead to high social and economic costs.
- Violence against women can have fatal results like homicide or suicide.
- It can lead to injuries, with 42% of women who experience intimate partner violence reporting an injury as a consequence of this violence.
- Intimate partner violence and sexual violence can lead to unintended pregnancies, induced abortions, gynecological problems, and sexually transmitted infections, including HIV. The 2013 analysis found that women who had been physically or sexually abused were 1.5 times more likely to have a sexually transmitted infection and, in some regions, HIV, compared to women who had not experienced partner violence. They are also twice as likely to have an abortion.
- Intimate partner violence in pregnancy also increases the likelihood of miscarriage, stillbirth, pre-term delivery and low birth weight babies.
- These forms of violence can lead to depression, post-traumatic stress disorder, sleep difficulties, eating disorders, emotional distress and suicide attempts. The same study found that women who have experienced intimate partner violence were almost twice as likely to experience depression and problem drinking. The rate was even higher for women who had experienced non partner sexual violence.
- Health effects can also include headaches, back pain, abdominal pain, fibromyalgia, gastrointestinal disorders, limited mobility and poor overall health.
- Sexual violence, particularly during childhood, can lead to increased smoking, drug and alcohol misuse, and risky sexual behaviors in later life. It is also associated with perpetration of violence (for males) and being a victim of violence (for females).

Impact on children
- Children who grow up in families where there is violence may suffer a range of behavioral and emotional disturbances. These can also be associated with perpetrating or experiencing violence later in life.
- Intimate partner violence has also been associated with higher rates of infant and child mortality and morbidity (e.g. diarrheal disease, malnutrition).

Social and economic costs

The social and economic costs of intimate partner and sexual violence are enormous and have ripple effects throughout society. Women may suffer isolation, inability to work, loss of wages, lack of participation in regular activities and limited ability to care for themselves and their children.

Prevention and response

Currently, there are few interventions whose effectiveness has been proven through well designed studies. More resources are needed to strengthen the prevention of intimate partner and sexual violence, including primary prevention, i.e. stopping it from happening in the first place.

Regarding primary prevention, there is some evidence from high-income countries that school-based programs to prevent violence within dating relationships have shown effectiveness. However, these have yet to be assessed for use in resource-poor settings. Several other primary prevention strategies: those that combine microfinance with gender equality training; that promote communication and relationship skills within couples and communities; that reduce access to, and harmful use of alcohol; and that change cultural gender norms, have shown some promise but need to be evaluated further.

To achieve lasting change, it is important to enact legislation and develop policies that:
- address discrimination against women;
- promote gender equality;
- support women; and
- help to move towards more peaceful cultural norms.

An appropriate response from the health sector can play an important role in the prevention of violence. Sensitization and education of health and other service providers is therefore another important strategy. To address fully the consequences of violence and the needs of victims/ survivors requires a multi-sect oral response.

WHO actions

WHO, in collaboration with partners, is:

- building the evidence base on the size and nature of violence against women in different settings and supporting countries' efforts to document and measure this violence and its consequences. This is central to understanding the magnitude and nature of the problem at a global level and to initiate action in countries;
- strengthening research and research capacity to assess interventions to address partner violence
- developing technical guidance for evidence-based intimate partner and sexual violence prevention and for strengthening the health sector responses to such violence;
- disseminating information and supporting national efforts to advance women's health and rights and the prevention of and response to violence against women;
- supporting countries' to strengthen the health sector response to violence against women, including the implementation of WHO tools and guidelines; and
- collaborating with international agencies and organizations to reduce/eliminate violence globally.

5. CARDIOVASCULAR DISEASES (CVDs)

Overview

Cardiovascular disease is caused by disorders of the heart and blood vessels, and includes coronary heart disease (heart attacks), cerebrovascular disease (stroke), raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. The major causes of cardiovascular disease are tobacco use, physical inactivity, an unhealthy diet and harmful use of alcohol.

Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots. The cause of heart attacks and strokes are usually the presence of a combination of risk factors, such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, hypertension, diabetes and hyperlipidemia.

KEY FACTS

- CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause.
- An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke .
- Over three quarters of CVD deaths take place in low- and middle-income countries.
- Out of the 16 million deaths under the age of 70 due to noncommunicable diseases, 82% are in low and middle income countries and 37% are caused by CVDs.
- Most cardiovascular diseases can be prevented by addressing behavioral risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies.
- People with cardiovascular disease or who are at high cardiovascular risk (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidemia or already established disease), need early detection and management using counselling and medicines, as appropriate.

What are cardiovascular diseases?

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels and they include:

- coronary heart disease – disease of the blood vessels supplying the heart muscle;
- cerebrovascular disease – disease of the blood vessels supplying the brain;
- peripheral arterial disease – disease of blood vessels supplying the arms and legs;
- rheumatic heart disease – damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria;
- congenital heart disease – malformations of heart structure existing at birth;
- deep vein thrombosis and pulmonary embolism – blood clots in the leg veins, which can dislodge and move to the heart and lungs.

What are the risk factors for cardiovascular disease?

The most important behavioral risk factors of heart disease and stroke are unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol. The effects of behavioral risk factors may show up in individuals as raised blood pressure, raised blood glucose, raised blood lipids, and overweight and obesity. These "intermediate risks factors" can be measured in primary care facilities and indicate an increased risk of developing a heart attack, stroke, heart failure and other complications.

Cessation of tobacco use, reduction of salt in the diet, consuming fruits and vegetables, regular physical activity and avoiding harmful use of alcohol have been shown to reduce the risk of cardiovascular disease. In addition, drug treatment of diabetes, hypertension and high blood lipids may be necessary to reduce cardiovascular risk and prevent heart attacks and strokes. Health policies that create conducive environments for making healthy choices affordable and available are essential for motivating people to adopt and sustain healthy behavior.

There are also a number of underlying determinants of CVDs or "the causes of the causes". These are a reflection of the major forces driving social, economic and cultural change – globalization, urbanization and population ageing. Other determinants of CVDs include poverty, stress and hereditary factors.

What are common symptoms of cardiovascular diseases?

Symptoms of heart attacks and strokes :

Often, there are no symptoms of the underlying disease of the blood vessels. A heart attack or stroke may be the first warning of underlying disease. Symptoms of a heart attack include:

- pain or discomfort in the centre of the chest;
- pain or discomfort in the arms, the left shoulder, elbows, jaw, or back.
- In addition the person may experience difficulty in breathing or shortness of breath; feeling sick or vomiting; feeling light-headed or faint; breaking into a cold sweat; and becoming pale. Women are more likely to have shortness of breath, nausea, vomiting, and back or jaw pain.

The most common symptom of a stroke is sudden weakness of the face, arm, or leg, most often on one side of the body. Other symptoms include sudden onset of:

- numbness of the face, arm, or leg, especially on one side of the body;
- confusion, difficulty speaking or understanding speech;
- difficulty seeing with one or both eyes;
- difficulty walking, dizziness, loss of balance or coordination;
- severe headache with no known cause; and
- fainting or unconsciousness.

People experiencing these symptoms should seek medical care immediately.

What is rheumatic heart disease?

Rheumatic heart disease is caused by damage to the heart valves and heart muscle from the inflammation and scarring caused by rheumatic fever. Rheumatic fever is caused by an abnormal response of the body to infection with streptococcal bacteria, which usually begins as a sore throat or tonsillitis in children. Rheumatic fever mostly affects children in developing countries, especially where poverty is widespread. Globally, about 2% of deaths from cardiovascular diseases is related to rheumatic heart disease.

Symptoms of rheumatic heart disease

- Symptoms of rheumatic heart disease include: shortness of breath, fatigue, irregular heartbeats, chest pain and fainting.
- Symptoms of rheumatic fever include: fever, pain and swelling of the joints, nausea, stomach cramps and vomiting.

Why are cardiovascular diseases a development issue in low- and middle-income countries?

- At least three quarters of the world's deaths from CVDs occur in low- and middle-income countries.
- People in low- and middle-income countries often do not have the benefit of integrated primary health care programs for early detection and treatment of people with risk factors compared to people in high-income countries.
- People in low- and middle-income countries who suffer from CVDs and other noncommunicable diseases have less access to effective and equitable health care services which respond to their needs. As a result, many people in low- and middle-income countries are detected late in the course of the disease and die younger from CVDs and other noncommunicable diseases, often in their most productive years.
- The poorest people in low- and middle-income countries are affected most. At the household level, sufficient evidence is emerging to prove that CVDs and other noncommunicable diseases contribute to poverty due to catastrophic health spending and high out-of-pocket expenditure.
- At macro-economic level, CVDs place a heavy burden on the economies of low- and middle-income countries.

How can the burden of cardiovascular diseases be reduced?

"Best buys" or very cost effective interventions that are feasible to be implemented even in low-resource settings have been identified by WHO for prevention and control of cardiovascular diseases. They include two types of interventions: population-wide and individual, which are recommended to be used in combination to reduce the greatest cardiovascular disease burden.

Examples of population-wide interventions that can be implemented to reduce CVDs include:
- comprehensive tobacco control policies
- taxation to reduce the intake of foods that are high in fat, sugar and salt
- building walking and cycle paths to increase physical activity
- strategies to reduce harmful use of alcohol
- providing healthy school meals to children.

At the individual level, for prevention of first heart attacks and strokes, individual health-care interventions need to be targeted to those at high total cardiovascular risk or those with single risk factor levels above traditional thresholds, such as hypertension and hypercholesterolemia. The former approach is more cost-effective than the latter and has the potential to substantially reduce cardiovascular events. This approach is feasible in primary care in low-resource settings, including by non-physician health workers.

For secondary prevention of cardiovascular disease in those with established disease, including diabetes, treatment with the following medications are necessary:
- aspirin
- beta-blockers
- angiotensin-converting enzyme inhibitors
- statins.

The benefits of these interventions are largely independent, but when used together with smoking cessation, nearly 75% of recurrent vascular events may be prevented. Currently there are major gaps in the implementation of these interventions particularly at the primary health care level.

In addition, costly surgical operations are sometimes required to treat CVDs. They include:
- coronary artery bypass
- balloon angioplasty (where a small balloon-like device is threaded through an artery to open the blockage)
- valve repair and replacement
- heart transplantation
- artificial heart operations

Medical devices are required to treat some CVDs. Such devices include pacemakers, prosthetic valves, and patches for closing holes in the heart.

WHO response

Reducing the incidence of hypertension by implementing population-wide policies to reduce behavioral risk factors, including harmful use of alcohol, physical inactivity, overweight, obesity and high salt intake, is essential to attaining this target. A total-risk approach needs to be adopted for early detection and cost-effective management of hypertension in order to prevent heart attacks, strokes and other complications.

The eighth target in the Global NCD action plan states at least 50% of eligible people should receive drug therapy and counseling (including glycemic control) to prevent heart attacks and strokes. Prevention of heart attacks and strokes through a total cardiovascular risk approach is more cost-effective than treatment decisions based on individual risk factor thresholds only and should be part of the basic benefits package for pursuing universal health coverage. Achieving this target will require strengthening key health system components, including health-care financing to ensure access to basic health technologies and essential NCD medicines.

6. DIOXINS AND THEIR EFFECTS ON HUMAN HEALTH

Overview

Dioxins are environmental pollutants. They belong to the so-called "dirty dozen" - a group of dangerous chemicals known as persistent organic pollutants (POPs). Dioxins are of concern because of their highly toxic potential. Experiments have shown they affect a number of organs and systems.

Once dioxins enter the body, they last a long time because of their chemical stability and their ability to be absorbed by fat tissue, where they are then stored in the body. Their half-life in the body is estimated to be 7 to 11 years. In the environment, dioxins tend to accumulate in the food chain. The higher an animal is in the food chain, the higher the concentration of dioxins.

KEY FACTS
- Dioxins are a group of chemically-related compounds that are persistent environmental pollutants (POPs).
- Dioxins are found throughout the world in the environment and they accumulate in the food chain, mainly in the fatty tissue of animals.
- More than 90% of human exposure is through food, mainly meat and dairy products, fish and shellfish. Many national authorities have programs in place to monitor the food supply.
- Dioxins are highly toxic and can cause reproductive and developmental problems, damage the immune system, interfere with hormones and also cause cancer.

- Due to the omnipresence of dioxins, all people have background exposure, which is not expected to affect human health. However, due to the highly toxic potential, efforts need to be undertaken to reduce current background exposure.
- Prevention or reduction of human exposure is best done via source-directed measures, i.e. strict control of industrial processes to reduce formation of dioxins.

Introduction

The chemical name for dioxin is: 2, 3, 7, 8-tetrachlorodibenzo para dioxin (TCDD). The name "dioxins" is often used for the family of structurally and chemically related polychlorinated dibenzo para dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Certain dioxin-like polychlorinated biphenyls (PCBs) with similar toxic properties are also included under the term "dioxins". Some 419 types of dioxin-related compounds have been identified but only about 30 of these are considered to have significant toxicity, with TCDD being the most toxic.

Sources of dioxin contamination

Dioxins are mainly by-products of industrial processes but can also result from natural processes, such as volcanic eruptions and forest fires. Dioxins are unwanted by-products of a wide range of manufacturing processes including smelting, chlorine bleaching of paper pulp and the manufacturing of some herbicides and pesticides. In terms of dioxin release into the environment, uncontrolled waste incinerators (solid waste and hospital waste) are often the worst culprits, due to incomplete burning. Technology is available that allows for controlled waste incineration with low dioxin emissions.

Although formation of dioxins is local, environmental distribution is global. Dioxins are found throughout the world in the environment. The highest levels of these compounds are found in some soils, sediments and food, especially dairy products, meat, fish and shellfish. Very low levels are found in plants, water and air.

Extensive stores of PCB-based waste industrial oils, many with high levels of PCDFs, exist throughout the world. Long-term storage and improper disposal of this material may result in dioxin release into the environment and the contamination of human and animal food supplies. PCB-based waste is not easily disposed of without contamination of the environment and human populations. Such material needs to be treated as hazardous waste and is best destroyed by high temperature incineration in specialized facilities.

Dioxin contamination incidents

Many countries monitor their food supply for dioxins. This has led to early detection of contamination and has often prevented impact on a larger scale. In many instances, dioxin contamination is introduced via contaminated animal feed, e.g. incidences of increased dioxin levels in milk or animal feed were traced back to clay, fat or citrus pulp pellets used in the production of the animal feed.

Some dioxin contamination events have been more significant, with broader implications in many countries.

In late 2008, Ireland recalled many tons of pork meat and pork products when up to 200 times the safe limit of dioxins were detected in samples of pork. This led to one of the largest food recalls related to a chemical contamination. Risk assessments performed by Ireland indicated no public health concern. The contamination was traced back to contaminated feed.

In 1999, high levels of dioxins were found in poultry and eggs from Belgium. Subsequently, dioxin-contaminated animal-based food (poultry, eggs, pork) were detected in several other countries. The cause was traced to animal feed contaminated with illegally disposed PCB-based waste industrial oil.

Large amounts of dioxins were released in a serious accident at a chemical factory in Seveso, Italy, in 1976. A cloud of toxic chemicals, including TCDD, was released into the air and eventually contaminated an area of 15 square kilometers where 37 000 people lived.

Extensive studies in the affected population are continuing to determine the long-term human health effects from this incident. TCDD has also been extensively studied for health effects linked to its presence as a contaminant in some batches of the herbicide Agent Orange, which was used as a defoliant during the Vietnam War. A link to certain types of cancers and also to diabetes is still being investigated.

Although all countries can be affected, most contamination cases have been reported in industrialized countries where adequate food contamination monitoring, greater awareness of the hazard and better regulatory controls are available for the detection of dioxin problems.

A few cases of intentional human poisoning have also been reported. The most notable incident is the 2004 case of Viktor Yushchenko, President of Ukraine, whose face was disfigured by chloracne.

Effects of dioxins on human health

Short-term exposure of humans to high levels of dioxins may result in skin lesions, such as chloracne and patchy darkening of the skin, and altered liver function. Long-term exposure is linked to impairment

of the immune system, the developing nervous system, the endocrine system and reproductive functions.

Chronic exposure of animals to dioxins has resulted in several types of cancer. TCDD was evaluated by the WHO's International Agency for Research on Cancer (IARC) in 1997 and 2012. Based on animal data and on human epidemiology data, TCDD was classified by IARC as a "known human carcinogen". However, TCDD does not affect genetic material and there is a level of exposure below which cancer risk would be negligible.

Due to the omnipresence of dioxins, all people have background exposure and a certain level of dioxins in the body, leading to the so-called body burden. Current normal background exposure is not expected to affect human health on average. However, due to the high toxic potential of this class of compounds, efforts need to be undertaken to reduce current background exposure.

Sensitive groups

The developing fetus is most sensitive to dioxin exposure. Newborn, with rapidly developing organ systems, may also be more vulnerable to certain effects. Some people or groups of people may be exposed to higher levels of dioxins because of their diet (such as high consumers of fish in certain parts of the world) or their occupation (such as workers in the pulp and paper industry, in incineration plants, and at hazardous waste sites).

Prevention and control of dioxin exposure

Proper incineration of contaminated material is the best available method of preventing and controlling exposure to dioxins. It can also destroy PCB-based waste oils. The incineration process requires high temperatures, over 850°C. For the destruction of large amounts of contaminated material, even higher temperatures - 1000°C or more - are required.

Prevention or reduction of human exposure is best done via source-directed measures, i.e. strict control of industrial processes to reduce formation of dioxins as much as possible. This is the responsibility of national governments. The Codex Alimentarius Commission adopted a Code of Practice for Source Directed Measures to Reduce Contamination of Foods with Chemicals (CAC/RCP 49-2001) in 2001. Later in 2006 a Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Food and Feeds (CAC/RCP 62-2006) was adopted.

More than 90% of human exposure to dioxins is through the food supply, mainly meat and dairy products, fish and shellfish. Therefore, protecting the food supply is critical. In addition to source-directed measures to reduce dioxin emissions, secondary contamination of the food supply needs to be avoided throughout the food chain. Good controls and practices during primary production, processing, distribution and sale are all essential in the production of safe food.

As indicated through the examples listed above, contaminated animal feed is often the root-cause of food contamination.

Food and feed contamination monitoring systems must be in place to ensure that tolerance levels are not exceeded. It is the responsibility of feed and food producers to assure safe raw materials and safe processes during production, and it is the role of national governments to monitor the safety of food supply and to take action to protect public health. When contamination is suspected, countries should have contingency plans to identify, detain and dispose of contaminated feed and food. The affected population should be examined in terms of exposure (for example, measuring the contaminants in blood or human milk) and effects (for example, clinical surveillance to detect signs of ill health).

What should consumers do to reduce their risk of exposure?

Trimming fat from meat and consuming low fat dairy products may decrease the exposure to dioxin compounds. Also, a balanced diet (including adequate amounts of fruits, vegetables and cereals) will help to avoid excessive exposure from a single source. This is a long-term strategy to reduce body burdens and is probably most relevant for girls and young women to reduce exposure of the developing fetus and when breastfeeding infants later on in life. However, the possibility for consumers to reduce their own exposure is somewhat limited.

What does it take to identify and measure dioxins in the environment and food?

The quantitative chemical analysis of dioxins requires sophisticated methods that are available only in a limited number of laboratories around the world. The analysis costs are very high and vary according to the type of sample, but range from over US$ 1000 for the analysis of a single biological sample to several thousand US dollars for the comprehensive assessment of release from a waste incinerator.

Increasingly, biological (cell- or antibody) -based screening methods are being developed, and the use of such methods for food and feed samples is increasingly being validated. Such screening methods allow more analyses at a lower cost, and in case of a positive screening test, confirmation of results must be carried out by more complex chemical analysis.

WHO activities related to dioxins

WHO published in 2015 for the first time estimates of the global burden of food borne disease. Dioxins' effects on fertility and on thyroid function were considered in this context, and only considering these 2 endpoints shows that this exposure can contribute significantly to food borne disease burden in some parts of the world.

Reducing dioxin exposure is an important public health goal for disease reduction. To provide guidance on acceptable levels of exposure, WHO has held a series of expert meetings to determine a tolerable intake of dioxins.

In 2001, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) performed an updated comprehensive risk assessment of PCDDs, PCDFs, and "dioxin-like" PCBs.

In order to assess long- or short-term risks to health due to these substances, total or average intake should be assessed over months, and the tolerable intake should be assessed over a period of at least 1 month. The experts established a provisional tolerable monthly intake (PTMI) of 70 picogram/kg per month. This level is the amount of dioxins that can be ingested over lifetime without detectable health effects.

WHO, in collaboration with FAO, through the Codex Alimentarius Commission, has established a 'Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Foods and Feed'. This document gives guidance to national and regional authorities on preventive measures.

WHO is also responsible for the Global Environment Monitoring System's Food Contamination Monitoring and Assessment Program. Commonly known as GEMS/Food, the program provides information on levels and trends of contaminants in food through its network of participating laboratories in over 50 countries around the world. Dioxins are included in this monitoring program.

WHO also conducted periodic studies on levels of dioxins in human milk. These studies provide an assessment of human exposure to dioxins from all sources. Recent exposure data indicate that measures introduced to control dioxin release in a number of developed countries have resulted in a substantial reduction in exposure over the past 2 decades. Data from developing countries are incomplete and do not allow yet a time-trend analysis.

WHO has established and regularly re-evaluated toxic equivalency factors (TEFs) for dioxins and related compounds through expert consultations. WHO-TEF values have been established which apply to humans, mammals, birds and fish.

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