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Original Article

Risk factors for urinary tract infections after one stage percutaneous nephrolithotomy

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ABSTRACT

Objective: To evaluate the risk factors for urinary tract infections (UTI) and the microorganism distribution in patients who underwent one stage percutaneous nephrolithotomy (PCNL)
Design: Retrospective study
Setting: Sakarya Training and Research Hospital, Sakarya, Turkey and Tepecik Training and Research Hospital, Izmir, Turkey
Subjects: From May 2013 to March 2018, 222 renal stones were obtained from patients who underwent one stage PCNL
Intervention: PCNL
Main outcome measures: UTI was defined as a body temperature of ≥38.5 °C persisting after 48 hours postoperatively with bacteriuria within one week after the operation. Patients were divided into two groups: Group A includes patients who developed UTI and Group B includes patients who did not. Our study compared the gender, patient age, diabetes, preop positive urine culture, hospital stay time, operation time, stone burden, acsess number, residual stone and stone hounsfield unit measured on non-contrast computed tomography in both groups.
Results: The study included 222 patients who matched the inclusion criteria (38 patients in group A and 184 patients in group B). The most common pathogen was *E. coli*, followed by enterococcus, pseudomonas, klebsiella, and staphylococcus. From univariate analysis, stone burden, operation time, acsess number and female sex were found to be the predictors of UTI after PCNL. Multivariate logistic regression analysis showed female sex and acsess number were associated with UTI after PCNL development.
Conclusions: We found that about 17% of patients developed UTI after single-stage PCNL despite antibiotic prophylaxis. Our study shows the risk factors of postoperative UTI include female sex and acsess number.

KEY WORDS: percutaneous nephrolithotomy, renal stone, urinary tract infections

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is a minimally invasive and gold standard surgical treatment for patients with large renal stones[1,2]. Even so, complications following this procedure are still common[2,3]. Although asepsis and antisepsis rules are administered in the surgical treatment, postoperative infections occur in up to 40% of cases[4-6]. More importantly, sepsis is rare (0.9-7.6%) after PCNL but is the leading cause of the high death rate (66-80%)[3-7]. In addition, postoperative infectious complications requiring additional antibiotic treatment and prolonged hospitalization can potentially be observed after PCNL[8]. Therefore, an understanding of the risk factors for infection after PCNL is of importance for the prevention and treatment of morbidity and mortality.

We aim to evaluate the risk factors of urinary tract infections (UTI) and the microorganism distribution in patients who underwent one stage PCNL in this study.

SUBJECTS AND METHODS

Two hundred and twenty-two renal stones were obtained from patients who underwent one stage PCNL between May 2013 and March 2018. Patients

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Dr. Salih Budak, Urology Clinic, Sakarya Training and Research Hospital, 2968 ada Baytur Korukent sitesi Nilüfer 5 D: 16 Korucuk mh. Adapazarı, Sakarya, Izmir, Turkey. Tel: +90 5052639870; Office: 0(264) 8884000; Fax: +90 2324330756; E-mail: salihbudak1977@gmail.com

eligible for inclusion in the study were all those who were candidates for PCNL treatment as the primary indication. Patients younger than 18 years of age were excluded from the study.

PCNL surgeries for all patients were performed under general anaesthesia. An open-ended urethral catheter was placed and advanced to the renal pelvis or the upper ureter with the patient in the supine lithotomy position. After placing the catheter, the patient was placed in the prone position and the kidney was accessed using an 18-gauge metal needle under C-arm fluoroscopic guidance. A guide wire was inserted into the collecting system via the lumen of the needle. One-stage PCNL was then performed using an Amplatz dilatation set. Following facial dilatation using a 10-F dilatator, the caliceal entrance was directly accessed using a 26-30 F facial dilatator. Multiple tract access are often a requirement in the presence of a large number of complex renal stones, staghorn calculus and residual calculus.

Preoperative urine culture (UC) was obtained from all patients who underwent PCNL in our clinic. In PCNL patients with negative UC results, the patient was given an intravenous broad spectrum antibiotic (cefuroxime or ciprofloxacin) at the time of anesthesia induction and 12 hours after the initial dose on the day of the procedure. Patients who had positive UC (greater than 100,000 cfu/ml) were treated with appropriate antibiotics based on sensitivity profile for at least two weeks. If control UC was sterile, intravenous broad spectrum antibiotic was applied. Otherwise, appropriate antibiotic suppression treatment was performed for at least seven days according to positive UC prior to PCNL.

UTI was defined as a body temperature of ≥38.5 °C persisting after 48 hours postoperatively with bacteriuria within one week after the operation. Significant bacteriuria was defined as ≥100,000 colony-forming units uropathogens/mL. Patients were divided into two groups: Group A includes patients who developed UTI and Group B includes patients who did not. Our study compared the gender, patient age (years), diabetes, preop positive UC, hospital stay time (days), operation time (mins), hemoglobin change amount (g/dl), stone burden (mm^2), acsess number, American Society of Anesthesiologists score, residual stone and stone hounsfield unit measured on non-contrast computed tomography.

In the control made with non-contrast computed tomography at postoperative first month, patients who had a stone larger than 4 mm were accepted as residual stone. Hospital stay time was calculated from the day prior to surgery until the day of discharge. Hemoglobin change was calculated according to the formula; preoperative hemoglobin tested one day before surgery and hemoglobin tested during postoperative 24 hours (hemoglobin change = preop-postop ±SD g/dl). Stone burden was calculated using the formula: Maximum diameter * width * p * ¼. Stones were classified as simple (isolated renal pelvis or isolated calyceal stones) or multiple (partial or complete staghorn stones, renal pelvis stones with accompanying calyceal stones) regardless of size.

For statistical analysis, data were compared using the Mann-Whitney U Test and Pearson Chi-Square test. $P<.05$ was accepted as statistically significant. Multiple logistic regression analysis was used to predict the factors affecting success.

Table 1: Demographic characteristics of patients and risk factors with UTI

Parameter	Group A (n = 38)	Group B (n = 184)	*P*
Age (years)			.202[a]
Median (Min-Max)	54.5(18-78)	56.5 (18-79)	
Mean±SS	50.1 ± 14.981	53.5 ± 14.836	
Stone burden			.001[a]
Median (Min-Max)	495(170-2464)	322.5 (112-2772)	
Mean±SS	685.1 ± 541.481	446.79 ± 387.21	
HU			.074[a]
Median (Min-Max)	870.5 (408-1451)	1050 (225 - 1915)	
Mean ± SS	887.7 ± 364.53	990.2 ± 379.76	
Gender n(%)			.022[a]
Female	21(55.3%)	65 (35.3%)	
Male	17(44.7%)	119 (64.7%)	
Stone Side n (%)			.838[b]
Right	17 (44.7)	79 (42.9%)	
Left	21 (55.2)	105 (57.1)	
Diabetes n (%)			.121[b]
No	26 (68.4%)	147 (79.9%)	
Yes	12 (31.6%)	37 (20.1%)	
ASA score n (%)			.319[b]
ASA1	19 (50%)	68 (37%)	
ASA2	15 (39.5%)	94 (51.1%)	
ASA3	4 (10.5)	22 (12%)	
Simple/Multiple n (%)			.192[b]
Simple	15 (39.5%)	94 (51.1%)	
Multiple	23 (60.5%)	90 (48.9%)	
Hospital stay time			.072[a]
Median (Min-Max)	3(1-14)	3 (1-14)	
Mean ± SS	3.89 ± 2.902	3.89 ± 2.902	.006[a]
Operation time			
Median (Min-Max)	102.5 (60-180)	85 (40 - 230)	
Mean ± SS	109.1 ± 33.729	93.5 ± 37.194	
Hgb change amount			.242[a]
Median (Min-Max)	1.9(-0.3-5.3)	1.5 (-0.8-8.7)	
Mean ± SS	1.94 ± 1.32	1.73 ± 1.376	
Acsess number			<.001[a]
Median (Min-Max)	1(1-4)	1(1-3)	
Mean ± SS	1.58 ± 0.826	1.15 ± 0.403	
Residual stone n(%)			.439[b]
No	24 (63.2%)	128 (69.6%)	
Yes	14 (36.8%)	56 (30.4%)	
Positive preoperative UC n(%)			.539[b]
Steril	28 (73.7%)	144 (78.3%)	
Yes	10 (26.3%)	40 (21.7%)	

[a]Mann-Whitney U Test; [b] Pearson Chi-Square Test
HU: Hounsfield Unit; ASA: American Society of Anesthesiologists; Hgb: hemoglobin; UC: urine culture

RESULTS

The study included 222 patients (86 women and 136 men) who matched the inclusion criteria. In the UTI Group A with 38 patients (21 women and 17 men), the mean age was 50.1±14.9 years. In Group B with 184 patients (65 women and 119 men), the mean age was 53.5±14.8 years. We found that 17.1% of patients developed UTI after one-stage PCNL despite antibiotic prophylaxis. Demographic characteristics of patients and correlation of risk factors with UTI are shown in Table 1. Multiple logistic regression analysis of variables associated with UTI after PCNL is given in Table 2. The distribution of microorganisms which are the UTI agent after PCNL are mentioned in Table 3. The most common pathogen was *E. coli*, followed by enterococcus, pseudomonas, klebsiella, and staphylococcus.

Table 2: Multiple logistic regression analysis of variables associated with UTI after PCNL.

Parameter	OR (95% CI)	*P*
Sex (female)	2.6 (1.14 - 5.95)	.024
Age (years)	0.98 (0.96 - 1.01)	.276
Stone burden	1.0 (1.0 - 1.002)	.121
HU	0.99 (0.99 - 1.0)	.192
Diabetes	1.56 (0.60 - 4.06)	.358
Operation time (mins)	1.0 (0.99 - 1.02)	.414
Hospital time	1.19 (0.98 - 1.46)	.084
Residual stone	0.67 (0.26 - 1.76)	.414
Positive preoperative UC	0.73 (0.29 - 1.93)	.528
Access number	3.03 (1.54 - 5.99)	.001

OR: odds ratio; CI: confidence interval; HU: Hounsfield Unit; UC: urine culture

At univariate analysis, stone burden (*P*=.001), operation time (*P*=.006), acsess number (*P*<.001) and female sex (*P*=.02) were found to be the predictors of UTI after PCNL. By multiple logistic regression analysis, female sex [OR=2.6, 95% CI=1.14–5.95, *P*=.024] and acsess number [OR=3.03, 95% CI=1.54–5.99, *P*=.001] were associated with UTI after PCNL development. Females are 2.6 times more likely to be infected than males. There were three patients who required intensive care and the mortality rate was zero.

DISCUSSION

Perioperative complications following this procedure are observed in up to one-third of patients[9]. PCNL is categorized as a clean-contaminated or contaminated surgery. Nevertheless, postoperative fever rate was 23% and infection after PCNL was 8%[10]. The American Urological Association guideline also recommends an appropriate prophylactic antibiotic for sterile urine preoperatively as a means of decreasing the incidence of postoperative sepsis[11].

Table 3: Frequency of micro-organisms in preoperative and postoperative positive urine cultures of percutaneous nephrolithotomy patients

Isolated micro-organism	Preop UC		Postop UC
	UTI (n=10, 26.3%)	Non-UTI (n=40, 21.7%)	UTI (n=38, 17.1%)
Escherichia coli	4	18	14 (36.8)
Pseudomonas spp.	2	5	7(18.4)
Klebsiella spp.	1	2	6 (15.8)
Enterococcus spp.	1	3	3 (7.9)
Staphylococcus	0	5	1(2.6)
Acinetobacter	0	0	2 (5.2)
Candida	0	1	1(2.6)
Mixed	2	6	4 (10.5)

UC: urine culture; UTI: urinary tract infection

Antibiotic prophylaxis fails to completely eliminate the risk of infection associated with the PCNL procedure[12]. This study included only patients who received preoperative antibiotic prophylaxis and who were positive for UC suppressed by appropriate antibiotics. Nevertheless, we found a 17.1% rate of UTI after PCNL. Previous studies have proposed a variety of antibiotics for prophylaxis[10-13]. Dogan *et al* compared antibiotic prophylaxis between a single preoperative intravenous dose of ofloxacin (200 mg) to a second group of patients who received treatment dose therapy (400 mg/day) until eventual removal of the nephrostomy tube. Results showed no differences between the two groups with respect to infection complications[10]. Mariappan *et al* has indicated that one week of ciprofloxacin prophylaxis prior to PCNL significantly reduced the risk of urosepsis[13].

Specific risk factors that are associated with postoperative UTI are positive intraoperative urine/stone culture, infected stone, neurogenic bladder, operative time and postoperative nephrostomy tube placement[14]. The CROES PCNL study group reviewed the incidence of UTI, postoperative fever and risk factors for post-PCNL fever from 96 centers[3]. This study investigated a total of 5803 patients and concluded that the predictors of the risk of infection post-PCNL include positive urine culture, female sex, operative time, hospital time, prior PCNL procedures and the pre-operative use of a nephrostomy tube[3]. Korets *et al* found that multivariate analysis controlling for gender, total stone burden greater than 10 cm^2, positive pelvic urine or stone cultures, and multiple renal pelvic punctures were risk factors[8]. Our results show the predictors of the risk of UTI after PCNL include female sex and acsess number.

Several studies have reported no relationship between gender and risk of postoperative fever in PCNL[5,12,13]. It has been reported that females are at a higher risk of postoperative UTI than males[3,8,13].

Daudon *et al* reports a higher proportion of calcium phosphate and Struvite stones in upper urinary tract stones in females than in males over all age groups[15]. Especially, calcium phosphate stones are often associated with UTI[15]. Acsess number will increase the probability of introducing more infective organisms into the system and will understandably increase the probability of postoperative UTI complications. In the study by Healy *et al*, the presence of staghorn calculi was shown to independently increase the risk of fever by approximately 60%[16]. In other studies, no correlation was found between staghorn stones and infection after PCNL[5,6].

In previous studies, several definitions were used in the literature to describe postoperative infection. In literature, postoperative fever[2,10,17], systemic inflammatory response syndrome (SIRS)[5,6,8,18], UTI [2,7,12], sepsis[2,6,10,13], and septic shock[3,19,20] results have been reported. Fever is a non-specific sign and may not necessarily be associated with infection and progressive systemic symptoms[12]. Postoperative fevers occur in up to 39.8% of patients who underwent PCNL, but most cases of fever following PCNL are minor and easily managed without intervention[5]. Although fever may be an indicator of post-PCNL infection, it could be related to other reasons such as atelectasis, release of inflammatory mediators or blood transfusion[17]. Several studies have reported the incidence of SIRS after PCNL to be 11.2–27.4% and the incidence of febrile UTI after PCNL to be 3.5-39.8%[5,6,7]. The differences among studies are likely related to highly variable definitions and methods of data collection[18]. SIRS criteria are available in many hospitalized patients, including those who do not develop infection, and often never cause adverse outcomes[21]. Nearly half of the patients undergoing PCNL met the criteria for SIRS within the first postoperative day[22]. We believe that the evaluation of SIRS or postoperative fever alone is inadequate to show the frequency of UTI after PCNL, like in other studies[5,8,14,15].

Sepsis was reported to be the most common cause of perioperative mortality after PCNL in large series[2,3]. Dogan *et al* has reported sepsis to occur in 1.5% of patients after PCNL, and none of the patients died of infectious complications[10]. On the other hand, Koras *et al* found that sepsis developed postoperatively in 7.6% of 303 patients undergoing PCNL[6]. Multiple definition and terminology for sepsis and septic shock are still in use, leading to differences in reported incidences and mortality[23]. In the present study, there were three patients who required intensive care, and the mortality rate was zero as in other studies[6,10].

The pathogenesis of postoperative UTI after PCNL begins with bacterial release through the nephrostomy tract after surgical manipulation[10,18]. Unfortunately, UC does not yield immediate results, and are usually obtained only after 48 hours. However, these results are beneficial if infection persists for more than 48 hours after surgery. While awaiting the UC result, the distribution of microorganisms according to previous studies may be helpful in starting treatment. In our study, *E. coli* was the predominant bacterial pathogen found in bladder urine (36.8%), similar to other studies[5,12]. This information is particularly useful in the selection of appropriate antibiotics to include Gram negative microorganisms in patients.

The retrospective design of our study and small sample size are the principal limitations. Details of antibiotic prophylaxis and UTI evaluation were not available, and therefore any potential variability in these factors was not considered in the analysis. Also, we did not study the stone composition.

CONCLUSION

In our study, we found that about 17% of patients developed urinary tract infection after one-stage percutaneous nephrolithotomy despite antibiotic prophylaxis. According to our results, risk factors of postoperative urinary tract infection include female sex and acsess number. Risks of postoperative urinary tract infection are preoperative urine culture sterile patients and patients with positive urine culture suppressed by appropriate antibiotics. However, microbiological evaluation is necessary for future management of probable infectious complications.

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REFERENCES

1. Ghani KR, Sammon JD, Bhojani N, Karakiewicz PI, Sun M, Sukumar S, *et al*. Trends in percutaneous nephrolithotomy use and outcomes in the United States. J Urol 2013; 190(2):558-564.
2. Armitage JN, Irving SO, Burgess NA, British Association of Urological Surgeons Section of Endourology. Percutaneous nephrolithotomy in the United Kingdom: Results of a prospective data registry. Eur Urol 2012; 61(6):1188-1193.
3. de la Rosette J, Assimos D, Desai M, Gutierrez J, Lingeman J, Scarpa R, *et al*. CROES PCNL Study Group.

The Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study: Indications, complications, and outcomes in 5803 patients. J Endourol 2011; 25(1):11-17
4. Paonessa JE, Gnessin E, Bhojani N, Williams JC Jr, Lingeman JE. Preoperative bladder urine culture as a predictor of intraoperative stone culture results: Clinical implications and relationship to stone composition. J Urol 2016; 196(3):769-774.
5. Draga RO, Kok ET, Sorel MR, Bosch RJ, Lock TM. Percutaneous nephrolithotomy: Factors associated with fever after the first postoperative day and systemic inflammatory response syndrome. J Endourol 2009; 23(6):921-927.
6. Koras O, Bozkurt IH, Yonguc T, Degirmenci T, Arslan B, Gunlusoy B, *et al*. Risk factors for postoperative infectious complications following percutaneous nephrolithotomy: A prospective clinical study. Urolithiasis 2015; 43(1):55-60.
7. Osman M, Wendt-Nordahl G, Heger K, Michel MS, Alken P, Knoll T. Percutaneous nephrolithotomy with ultrasonography-guided renal access: Experience from over 300 cases. BJU Int 2005; 96(6):875-878.
8. Korets R, Graversen JA, Kates M, Mues AC, Gupta M. Post-percutaneous nephrolithotomy systemic inflammatory response: A prospective analysis of preoperative urine, renal pelvic urine and stone cultures. J Urol 2011; 186:1899-1903.
9. Tefekli A, Karadag MA, Tepeler K, Sari E, Berberoglu Y, Baykal M, *et al*. Classification of percutaneous nephrolithotomy complications using the modified Clavien grading system: Looking for a standard. Eur Urol 2008; 53(1):184-190.
10. Dogan HS, Guliyev F, Cetinkaya YS, Sofikerim M, Ozden E, Sahin A. Importance of microbiological evaluation in management of infectious complications following percutaneous nephrolithotomy. Int Urol Nephrol 2007; 39(3):737-742.
11. Grabe M, Bjerklund-Johansen TE, Botto H, *et al*. EAU guidelines on urological infections 2013. Presented at: 28th Annual EAU Congress; March 15-19, 2013; Milan, Italy.
12. Gutierrez J, Smith A, Geavlete P, Shah H, Kural AR, de Sio M, *et al*. Urinary tract infections and post-operative fever in percutaneous nephrolithotomy. World J Urol 2013; 31(5):1135-1140.
13. Mariappan P, Smith G, Moussa SA, Tolley DA. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: A prospective controlled study. BJU Int 2006; 98(5):1075-1079.
14. Labate G, Modi P, Timoney A, Cormio L, Zhang X, Louie M, *et al*. The percutaneous nephrolithotomy global study: Classification of complications. J Endourol 2011; 25(8):1275-1280.
15. Daudon M, Dore JC, Jungers P, Lacour B. Changes in stone composition according to age and gender of patients: A multivariate epidemiological approach. Urol Res 2004; 23:241-247.
16. Healy KA, Ogan K. Pathophysiology and management of infectious staghorn calculi. Urol Clin North Am 2007; 34:363-374.
17. Troxel SA, Low KR. Renal intrapelvic pressure during percutaneous nephrolithotomy and its correlation with the development of postoperative fever. J Urol 2002; 168(4 Pt 1):1348-1351.
18. Churpek MM, Zadravecz FJ, Winslow C, Howell MD, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. Am J Respir Crit Care Med 2015; 192(8):958-964.
19. Gonen M, Turan H, Ozturk B, Ozkardes H. Factors affecting fever following percutaneous nephrolithotomy: A prospective clinical study. J Endourol 2008; 22(9):2135-2138.
20. Wang Y, Jiang F, Wang Y, Hou Y, Zhang H, Chen Q, *et al*. Post-percutaneous nephrolithotomy septic shock and severe hemorrhage: A study of risk factors. Urol Int 2012; 88(3):307-310.
21. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315(8):801-810.
22. Moses RA, Agarwal D, Raffin EP, Viers BR, Sharma V, Krambeck AE, *et al*. Postpercutaneous nephrolithotomy systemic ınflammatory response syndrome is not associated with unplanned readmission. Urology 2017; 100:33-37.
23. Violette PD, Denstedt JD. Standardizing the reporting of percutaneous nephrolithotomy complications. Indian J Urol 2014; 30:84-91.

Original Article

Disease modifying anti-rheumatic drug regimens for sustained remission in rheumatoid arthritis: Differences across the ethnic groups

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ABSTRACT

Objectives: The main purpose of this study was to determine the ethnic differences in the disease modifying anti-rheumatic drug (DMARD) regimens for sustained clinical remission among Malaysian rheumatoid arthritis (RA) patients.
Design: Cross sectional study
Setting: Tertiary hospitals in Malaysia
Subjects: All RA patients who were in clinical remission were consecutively recruited from the outpatient clinics of two tertiary hospitals in Malaysia from January to September 2017. The subjects were on conventional DMARDs and/or biologic therapy. Information on patients' disease duration, seropositivity, remission duration and medications were collected by reviewing the medical records.
Intervention: None (observational study)
Main outcome measures: Dose of DMARDs and the DMARD regimens across the ethnic groups
Results: A total of 124 subjects were recruited. The subjects were made up of the three main ethnic groups in Malaysia, *i.e.*, Malays (46%), Chinese (23.4%) and Indians (30.6%). The use of methotrexate and leflunomide were significantly higher among the Chinese with a frequency of 82.8% (P=.04) and 41.4% (P=.01), respectively. Besides, the mean methotrexate dose was significantly higher among the Chinese (11.4±6.6 mg/kg, P=.032). Malays recorded the lowest percentage for prednisolone (14%) but the highest for sulfasalazine (59.6%) and hydroxychloroquine (49.1%). Compared to the Malays and Chinese, the use of biologics was less frequent among the Indians (10.5%).
Conclusion: There appeared to be a distinctive pattern in the use of DMARDs across the main ethnic groups in Malaysia for sustained remission in RA.

KEY WORDS: DMARD, pharmacoethnicity, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive, systemic inflammatory disease which can lead to significant functional disability, diminished quality of life and premature mortality[1]. It is the most common inflammatory arthritis affecting 0.5-1% of the adult population[2]. In the past few decades, the treatment paradigm in RA has changed dramatically. Targeted therapies are introduced early to prevent joint damage and functional impairment.

RA is a heterogenous disease. Genetic factors tend to influence the course and severity of the disease. The type, dose and regimen of disease-modifying anti-rheumatic drugs (DMARDs) to achieve remission may significantly vary from one individual to another[3,4]. Such inter-individual differences in drug response may be due to genetic polymorphisms involving genes encoding enzymes and transporters of drug metabolism[5].

Some studies have suggested that polymorphisms in genes regulating the methotrexate (MTX) cellular pathway may determine the response to MTX, which

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is the anchor drug in RA. Allele frequencies tend to vary significantly across races and may influence the pharmacogenetics of DMARDs[5,6]. Apart from genes, certain factors such as medication adherence and cultural health beliefs could explain the inter-racial differences in drug regimens to induce remission in RA[3,7].

Malaysia is a multiracial country in southeast Asia consisting of Malays, Chinese, Indians and several indigenous ethnic groups. To date, there is a paucity of data on pharmacoethnicity of DMARD regimens for sustained remission in RA among Asians. This prompted us to conduct this study to determine the differences (if any) in the DMARD regimens among the three major ethnic groups in Malaysia, who were clinically in remission. A better understanding of pharmacoethnicity of DMARDs would pave the way for more personalized medicine in the treatment of RA.

SUBJECTS AND METHODS

Study design

From January to September 2017, all RA patients deemed to be in clinical remission by the attending rheumatologist were consecutively recruited from the outpatient clinics of Putrajaya Hospital and University Kebangsaan Malaysia Medical Centre in Malaysia. All patients were on conventional DMARDs and/or biologic therapy. Ethical approval was obtained from the institutional ethics committee and written consent was obtained from all patients.

Study population and protocol

All subjects had to fulfill the following criteria: (1) RA classified according to the American College of Rheumatology 2010 criteria; (2) aged 18 years and above; (3) in sustained remission with no flares of disease for at least six months prior to enrollment and; (4) stable treatment for six months. Patients with low disease activity were not included in order to achieve a more homogenous study population.

Patients were excluded if: (1) pregnant; (2) had an underlying renal or liver impairment; (3) diagnosed with malignancy or; 4) were of mixed parentage. The use of certain DMARDs such as MTX and leflunomide is an absolute contraindication in pregnancy and a relative contraindication in renal and liver impairment, depending on the severity.

All subjects were assessed for their disease activity based on 28-joint count Disease Activity Score. Clinical remission was defined as a 28 joint Disease Activity Score of ≤2.6 based on an established criteria[8]. Information on patients' disease duration, seropositivity, remission duration and medications were collected by reviewing the medical records.

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences software version 23. As this is primarily an exploratory analysis, no corrections have been made for multiple testing. Much emphasis was placed on descriptive statistics. The continuous variables were tested for normality using Kologorov Smirnov test. The continuous variables which were normally distributed were analyzed using one way ANOVA and expressed as mean with the standard deviation. The categorical variables were analyzed using the chi-square test. A *P*-value <.05 was considered significant.

RESULTS

Cohort characteristics

According to the census, there were 521 RA patients in total from both the study centres. A total of 124 subjects (23.8% of our cohort of RA patients) were recruited. The subjects were made up of the three main ethnic groups in Malaysia, *i.e.*, Malays (46%), Chinese (23.4%) and Indians (30.6%). The mean age was 57.5±10.24 years. The socio-demographic and clinical characteristics of the subjects are shown in Table 1. The vast majority of the subjects were women (79%) and had seropositive disease (76.6%). The mean disease duration was more than 10 years across the ethnic groups. The Chinese subjects had significantly higher mean duration in remission (50.5±45.5 months, *P*=.008) compared to the Malays and Indians.

Table 1: Characteristics of rheumatoid arthritis patients by ethnic group

Characteristics	Malay (n=57)	Indian (n=38)	Chinese (n=29)	Total	*P*-value
Age (years)	57.5 ± 9.2	55.5 ± 12.3	61.6 ± 8.2		.049
Gender, n (%)					
Female	47(82.5)	26 (68.4)	25 (86.2)	98 (79.0)	
Male	10 (17.5)	12 (31.6)	4 (13.8)	26 (21.0)	.143
Seropositive disease, n (%)	43 (75.4)	29 (76.3)	23 (79.3)	95 (76.6)	.921
Duration of disease (years)	11.3 ± 6.7	11.9 ± 4.7	13.8 ± 8.6		.268
Duration of remission (months)	28.8 ± 20.1	35.9 ± 28.1	50.5 ± 45.5		.008
Weight (kg)	67.3 ± 16.3	66.9 ± 15.9	55.8 ± 12.7		.003

Values are expressed as number (%) or mean ± SD.

Table 2: The use of DMARDs across the ethnic groups

RA treatment	Malay (n=57)	Indian (n=38)	Chinese (n=29)	Total	*P*-value
MTX, n (%)	32(56.1)	22(57.9)	24(82.8)	78(62.9)	.040
MTX dose, mean (mg/week)	7.5±7.8	7.1±6.9	11.4±6.6		
Sulfasalazine, n (%)	34(59.6)	13(34.2)	2(6.9)	49(39.5)	.032
Hydroxycholoroquine, n (%)	28(49.1)	14(36.8)	4(13.8)	46(37.1)	.075
Leflunomide, n (%)	22(38.6)	9 (23.68)	12 (41.4)	43(34.7)	
Biologic, n (%)	26 (45.6)	4 (10.5)	13 (44.8)	43(34.7)	.743
Prednisolone, n (%)	8 (14)	17 (44.7)	13 (44.8)	38(30.6)	
No. of DMARDs					.010
Single (%)	26(45.6)	21(55.3)	10(34.5)	57(46)	.383
Double (%)	23(40.4)	11(28.9)	17(58.6)	51(41.1)	.060
Triple (%)	1(1.8)	2(5.3)	1(3.4)	4(3.2)	
Prednisolone alone	7(12.3)	4(10.5)	1(3.4)	12(9.7)	.273

DMARDs: disease modifying anti-rheumatic drugs; RA: rheumatoid arthritis; MTX: methotrexate
Values are expressed as number (%) or mean ± SD.

DMARD therapy for sustained remission

Nearly half (46%) of the subjects in this cohort were on monotherapy for sustained remission. The most common DMARD in this regard was MTX. The biologics used by the subjects in this study included infliximab, adalimumab, etanercept and tocilizumab. None of the subjects were on janus kinase inhibitors. Apart from tocilizumab, the remaining biologics which were tumour necrosis factor inhibitors were prescribed along with MTX or leflunomide. Although 29% of the subjects were on steroid therapy, the highest dose was 5mg of prednisolone daily. The most common double DMARD combination regime was MTX with leflunomide, whereas triple DMARD therapy was MTX in combination with sulfasalazine and hydroxychloroquine.

DMARD regimens across the ethnic groups

The data on the use of DMARDS across the ethnic groups is presented in Table 2. The use of MTX and leflunomide were significantly higher among the Chinese with a frequency of 82.8% (*P*=.04) and 41.4% (*P*=.01), respectively. Besides, the mean MTX dose was significantly higher among the Chinese (11.4±6.6 mg/kg weekly, *P*=.032), although the Chinese had a lower mean body weight (55.8±12.7, *P*=.05) than the Malays and Indians.

The Malays recorded the lowest percentage for prednisolone (14%) but the highest for sulfasalazine (59.6%) and hydroxychloroquine (49.1%). Compared to the Malays and Chinese, the use of biologics was less frequent among the Indians (10.5%).

DISCUSSION

This study has revealed a distinctive pattern in the use of DMARDs across the main ethnic groups in Malaysia for sustained remission in RA. We found that the use of MTX and leflunomide were significantly higher among the Chinese patients. Besides, the mean dose of MTX was the highest among the Chinese despite having the lowest mean body weight. The use of MTX and leflunomide in RA is often complicated and limited by the development of transaminitis or non-alcoholic fatty liver disease[9]. The higher use of MTX and leflunomide among the Chinese may be explained by a Malaysian study which disclosed that the Chinese had the lowest prevalence of non-alcoholic fatty liver disease[10]. It is tempting to speculate that the Chinese subjects in this study could tolerate MTX and leflunomide more than the other ethnic groups owing to their significantly lower mean body weight**.** Of note, obesity is a major risk factor for non-alcoholic fatty liver disease[11].

Besides, the ethnic differences in the allele frequencies of the single-nucleotide polymorphisms in the methylenetetrahydrofolate reductase gene could influence the efficacy and toxicity of MTX[12]. Weisman *et al* reported that amino imidazole ribonucleotide transformylase 347GG genotype was associated with gastrointestinal intolerance of MTX[13].

Leflunomide and MTX have higher efficacy in controlling inflammation compared to sulfasalazine and hydroxychloroquine[14,15]. Despite the highest frequency for MTX and leflunomide among the Chinese, the use of prednisolone among them was also the highest. This suggests that the Malaysian Chinese RA patients require more potent DMARDs to maintain remission. There is a lack of Malaysian data on ethnic disparities with regard to disease severity in RA to support the above finding.

Although biologics have revolutionized the therapeutic armamentarium of RA in the recent decades, approximately only one third of the subjects were on biologics. Indians recorded the least use of this form of therapy. This may be partially explained by the reluctance to be on regular injections. In the Malaysian

context, it is a common perception that the Indian ethnic group has lower pain threshold[16]. However, this observation remains anecdotal. Furthermore, a small percentage of patients were on prednisolone alone, contrary to standard practice, due to various reasons such as DMARD intolerance due to allergic reactions, gastrointestinal side effects or personal preferences.

RA treatment approach is frequently based on joint decisions involving the rheumatologists, patients and their families. Patient preference for medications may account for the racial disparities in the DMARD regimen. Why treatment preferences differ by ethnicity, however, is not well understood. Nevertheless, our study certainly adds to the under-researched field of pharmacoethnicity in RA. Understanding the pharmacoethnicity in RA treatment is crucial to customize intervention programs for different racial groups. A tailored treatment approach may be more cost effective in the long run.

CONCLUSION

There appeared to be a distinctive pattern in the use of DMARDs across the main ethnic groups in Malaysia for sustained remission in RA. The use of MTX and leflunomide were significantly higher among the Chinese, whereas the use of sulfazalazine and hydroxychloroquine were significantly higher among the Malays.

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REFERENCES

1. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am 2001; 27(2):269-281.
2. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010; 376:1094-1108.
3. Constantinescu F, Goucher S, Weinstein A, Fraenkel L. Racial disparities in treatment preferences for rheumatoid arthritis. Med Care 2009; 47(3):350-355.
4. Bruce B, Fries JF, Murtagh KN. Health status disparities in ethnic minority patients with rheumatoid arthritis: A cross sectional study. J Rheumatol 2007; 34(7):1475-1479.
5. Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. Science 1999; 286(5439):487-491.
6. Brinker RR, Ranganathan P. Methotrexate pharmacogenetics in rheumatoid arthritis. Clin Exp Rheumatol 2010; 28(5 Suppl 61):S33-39.
7. Constantinescu F, Goucher S, Weinstein A, Smith W, Fraenkel L. Understanding why rheumatoid arthritis patient treatment preferences differ by race. Arthritis Rheum 2009; 61(4):413-418.
8. Fleischmann RM, van der Heijde D, Gardiner PV, Szumski A, Marshall L, Bananis E. DAS28-CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable. RMD Open 2017; 3(1):e000382.
9. Sakthiswary R, Chan GY, Koh ET, Leong KP, Thong BY. Methotrexate-associated nonalcoholic fatty liver disease with transaminitis in rheumatoid arthritis. The Scientific World Journal 2014; 2014:823763.
10. Goh SC, Ho EL, Goh KL. Prevalence and risk factors of non-alcoholic fatty liver disease in a multiracial suburban Asian population in Malaysia. Hepatol Int 2013; 7(2):548-554.
11. Karlas T, Wiegand J, Berg T. Gastrointestinal complications of obesity: non-alcoholic fatty liver disease (NAFLD) and its sequelae. Best Pract Res Clin Endocrinol Metab 2013; 27(2):195-208.
12. Hughes LB, Beasley TM, Patel H, Tiwari HK, Morgan SL, Baggott JE, *et al*. Racial or ethnic differences in allele frequencies of single-nucleotide polymorphisms in the methylenetetrahydrofolate reductase gene and their influence on response to methotrexate in rheumatoid arthritis. Ann Rheum Dis 2006; 65(9):1213-1218.
13. Weisman MH, Furst DE, Park GS, Kremer JM, Smith KM, Wallace DJ, *et al*. Risk genotypes in folate-dependent enzymes and their association with methotrexate-related side effects in rheumatoid arthritis. Arthritis Rheum 2006; 54(2):607-612.
14. Kaiden JR, Scott DL, Smolen JS, Schattenkirchner M, Rozman B, Williams BD, *et al*. Improved functional ability in patients with rheumatoid arthritis--longterm treatment with leflunomide versus sulfasalazine. European Leflunomide Study Group. J Rheumatol 2001; 28(9):1983-1991.
15. Smolen JS. Efficacy and safety of the new DMARD leflunomide: Comparison to placebo and sulfasalazine in active rheumatoid arthritis. Scand J Rheumatol Suppl 1999; 112:15-21.
16. Gupta ED, Zailinawati AH, Lim AW, Chan JB, Yap SH, Hla YY H, *et al*. Are Indians and females less tolerant to pain? An observational study using a laboratory pain model. Med J Malaysia 2009; 64(2):111-113.

Original Article

Immunohistochemical evaluation of microsatellite instability in colon polyps and colorectal cancers

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ABSTRACT

Objective: Colorectal cancers (CRCs) are among the most common malignancies. In 15% of these cases, there is a defect in the DNA mismatch repair pathway, which results in microsatellite instability (MSI). Conventional adenomatous lesions considered the precursors of CRCs also show MSI. Detection of MSI in adenomas is useful for early diagnosis of Lynch Syndrome. MSI is detected by molecular study. We attempted to immunohistochemically evaluate the MSI in colon cancer and polyps.
Design: Retrospective study
Setting: Department of Pathology, Mugla Sıtkı Kocman University Training and Research Hospital, Turkey
Subject: We performed immunohistochemical MSI analysis of 119 colon polyps and 88 conventional CRC patients who had materials in our hospital pathology laboratory between 2014 and 2017. For this purpose, the immune markers MLH1, MSH2, PMS2 and MSH6 were used. All statistical analyses were done with the SPSS 14.0 software. Paired comparisons were performed using the Independent Sample t test and one sample t test. $P<.05$ was considered statistically significant.
Intervention: None
Main outcome measures: MLH1, MSH2, PMS2 and MSH6 immunhistochemical markers of MSI and colon lesions
Results: We detected MSI in tubular and tubulovillous adenomas with high dysplastic content ($P=.05$) and left colonic localization ($P=.05$). We detected MSI predominanlty in female patients ($P=.05$), tumors with right colonic localization ($P=.05$), larger tumors ($P=.05$), advanced stage tumors ($P=.05$), and tumors with lymph node metastases ($P=.05$).
Conclusion: According to our findings, immunohistochemical MSI analysis may have a decisive role prior to molecular analysis in early colorectal lesions and CRCs.

KEY WORDS: colorectal lesions, immunohistochemistry, microsatellite instability

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide[1]. The mean age at diagnosis is 62 years. Eighty-five percent of CRCs are associated with chromosomal instability. In about 15% of cases, there is a defect in the DNA mismatch repair (MMR) pathway resulting in microsatellite instability (MSI), and 2-5% of cases are associated with hereditary nonpoliposis colorectal cancers (Lynch Syndrome)[2,3]. The loss of MMR activity results in a mutation which is responsible for the pathogenesis of MSI tumors[2,4].

Lynch syndrome (LS) is a common hereditary cancer susceptibility syndrome characterized by increased risk of colorectal, endometrial, gastric, ovarian, and other cancers[4]. Although early tumor development is a characteristic of LS, approximately 60% of colorectal cancers in LS may not be noticed before the age of 50[5]. Therefore, screening colorectal precursor lesions of LS detected at routine colonoscopy in fifties may help identify at-risk patients and family members before cancer development[6].

An alternative way to assess MMR is the analysis of DNA gene protein products (MLH1, MSH2, MSH6 and PMS2) by immunohistochemical staining[7]. Immunohistochemical analysis of MSI is a valuable tool. The National Comprehensive Cancer Network directives indicated a false negative rate for immunohistochemical analysis between 5% and 10%[8]. Determining MSI status provides prognostic and therapeutic information in the process of personalization of treatment of not only patients with LS, but also patients with sporadic CRC[9].

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Among colon polyps, conventional adenomas with tubular and villous properties with a high dysplastic content particularly show MSI, making MSI the main pathway in the genesis of conventional adenomas, and hence, cancer[10].

MSI analysis is less sensitive for detecting LS in conventional adenomas than advanced stage neoplasms. The estimated incidence of MSI among adenomas is 41-86% (mean 70%), and the immunohistochemical sensitivity is 49-82% (mean 72%)[11].

As MMR deficiency is an early event in colorectal tumor development, MSI screening is a useful strategy for early diagnosis of LS. Previous studies have shown that MMR deficiency had a sensitivity of 70% for LS adenomas[4,11].

In the present study, we assessed immunohistochemical expression of MLH1, MSH2, PMS2 and MSH6 in colonic polyps (tubular, tubulovillous, hyperplastic) and CRC cases (age, sex, localization, tumor size, stage, lymph node metastasis) from a time period between 2014 and 2017.

MATERIALS AND METHODS

A total of 88 conventional CRCs (42 women, 46 men) and 119 polyps (47 women and 72 men; 55 tubular, 40 hyperplastic, 24 tubulovillous) were included in this retrospective study. The age range of patients were 38-82 years in the CRC group and 25-82 years in the polyp group. Hospital archives were used to obtain information about tumors and clinical macroscopic progress. Ethical approval for the study was obtained from Ethics Committee of Mugla Sıtkı Kocman Üniversity Medical Training and Research Hospital (No:2982/2016)

The sections stained with hemotoxylin-eosin were examined by two pathologists. Cancer stage, lymphovascular and perineural invasion, lymph node metastases, polyp type, and dysplasia grade were determined. Lesion localization was either in right colon (caecum, ascending colon, transverse colon, hepatic flexura) or left colon (splenic flexura, descending colon, sigmoid colon, rectosigmoid and rectum). The histological differentiation grades and pathological stages of CRCs were determined on the basis of the World Health Organization 2010 classification of tumors of the digestive system[12].

All statistical analyses were done with the SPSS 14.0 software. Paired comparisons were performed using the Independent Sample t test and one sample t test.

Immunohistochemical analysis was carried out with MLH1 (Leica, ES05, 1;50), MSH2 (Leica, 25D12), PMS2 (Leica MOR4G, 1;100) and MSH6 (Leica, PU29, 1;100). Five-micron sections taken from blocs embedded in paraffin fixated with 10% formol were stained with an automatic Leica Bond branded immumohistochemical staining device. Normal mucosa and immune cells were used as positive internal controls. The presence and absence of nuclear staining was evaluated.

RESULTS

All hyperplastic polyps demonstrated positive staining with four markers. Among tubular and tubulovillous adenomas, 10 cases with severe dysplasia displayed negativity with one or several markers. Six of these samples were tubular adenomas and four were tubulovillous adenomas. Eight were located in the left side and two in the right side. A significant result was obtained with the left side and severe dysplasia (P=.05). The age range was 39-55 years. The size range was 5-30 mm.

All 19 CRCs showing MSI were conventional adenocarcinomas. Eleven of them were located in right colon and eight in left colon. Four CRCs had metastasized to lymph nodes. Twelve patients were female and seven were male, with an age range of 46-82 years. Fourteen were T3, three were T2 and one was T4. Eleven were stage 3, seven were stage 2 and one was stage 4.

Lymphovascular and perineural invasion and lymph node involvement were more common in poorly differentiated carcinomas in which the loss of the expression of immunohistochemical markers was

Table 1: Features of all CRCs and CRCs showing MSI

Features	CRCs showing MSI (n=19)	All of CRCs (N=88)
Location		
Right colon	11(57.9%)	41(46.59%)
Left colon	8(42.1%)	47(53.41%)
Sex		
Female	12(63.16%)	43(48.90%)
Male	7(36.84%)	45(51.10%)
Grade		
Grade 1	1(5.27%)	11(12.50%)
Grade 2	16(84.21%)	40(45.50%)
Grade 3	2(10.52%)	37(42.00%)
Tumor		
T1	1(5.26%)	12(13.63%)
T2	3(15.79%)	29(32.95%)
T3	14(73.69%)	39(44.32%)
T4	1(5.26%)	8(9.10%)
Lymph node metastasis		
Positive	4(21%)	12(13.64%)
Negative	15(78.9%)	76(86.36%)
Distant metastasis		
Positive	2(10.5%)	80(90.90%)
Negative	17(89.5%)	8(9.10%)

CRC: colorectal cancer; MSI: microsatellite instability

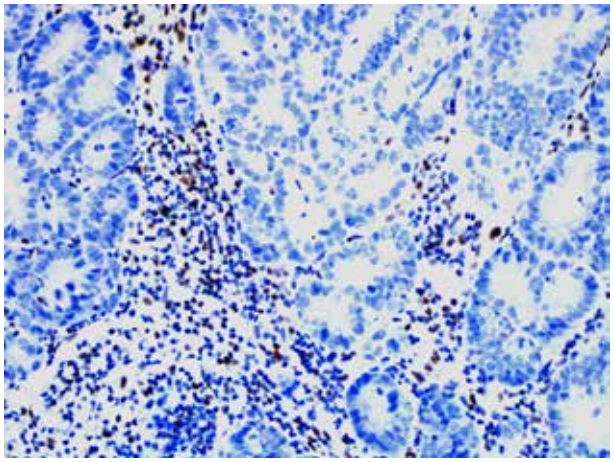

Fig 1: MLH1 controlled immuno expression negativity (x200)

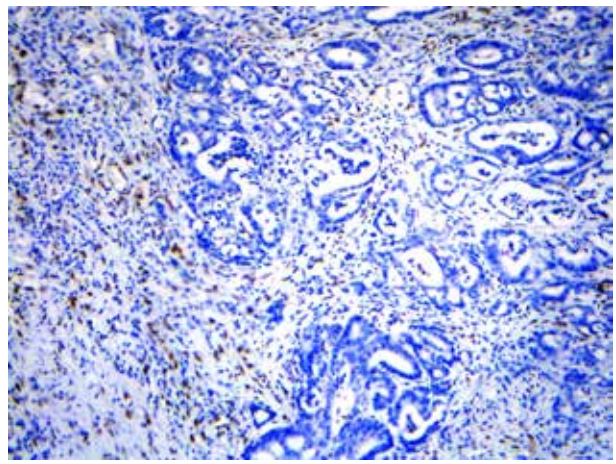

Fig 2: PMS2 controlled immuno expression negativity (x200)

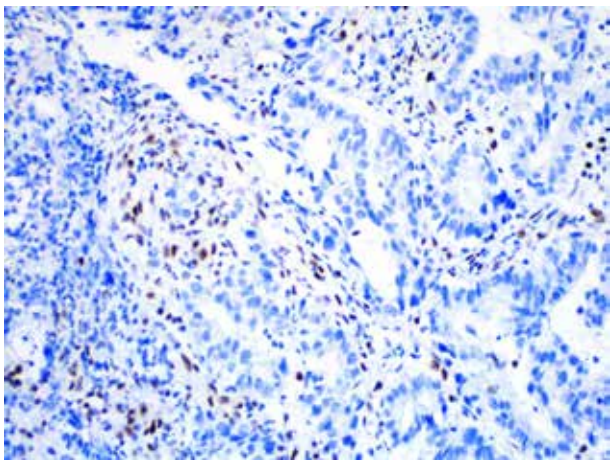

Fig 3: MSH2 controlled immuno expression negativity (x200)

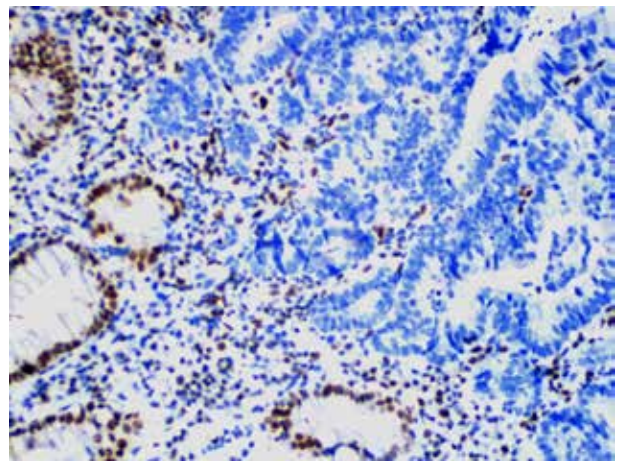

Fig 4: MSH6 controlled immuno expression negativity (x200)

more prominent. The loss of expression was greater, and lymphovascular invasion and lymph node involvement were clearly more common in right-sided cancers. The features of all CRCs and CRCs showing MSI are shown in Table 1.

In the immunohistochemical analysis, all four markers were negative (Figs 1-4) in five cases. Thirteen cases had combined negativity of MLH1 and PMS2. MSH2 and MSH6 were both negative in four cases. MLH1 alone was negative in two cases.

Statistically, right-side localization (*P*=.05), female gender (*P*=.05), tumor size increase (*P*=.05), advanced stage (*P*=.05) and lymph node metastases (*P*=.05) yielded significant results.

DISCUSSION

The majority of colon adenomas are detected during routine colonoscopic examination of asymptomatic persons aged 50-75 years[13]. As MMR deficiency is responsible for the early stages of colorectal tumorigenesis, MSI screening may be of use for the early detection of LS adenomas[6]. A strong correlation between MSI adenomas and LS was reported, but its exact cause is still unknown[6,14]. It has been reported that while sporadic colorectal cancers primarily arise through serratation, LS tumors arise from conventional adenomas (tubular, tubulovillous, villous)[15].

As MSI appears earlier in LS than sporadic cases during tumorogenesis period, it has been considered to be likely found in patients with LS. It has also been reported that the detection of MSI in precancerous lesions may be a marker of rapid tumor progression[7]. Some studies have found it at a lower rate in adenomas located in right colon[11,16]. Among our polyps, all hyperplastic ones were positively stained for MSI. Negativity with one or more markers was particularly common for adenomas with severe dysplasia, large size and left colonic localization.

MSI pathway is responsible for the pathogenesis of 15-17% of CRC cases[2,17]. Autosomal dominant LS occurs in the MSI pathway and is associated with an increased risk of tumor development at a young age[4]. Some authors recommend screening for protein loss in

spontaneous CRCs that have MSI but are non-familial to determine their prognosis and treatment response[18]. It is important to recognize tumors with MSI in order to diagnose LS, follow-up family members before clinical cancer arises and select appropriate treatment. As PCR-based techniques used for this purpose are expensive, immunohistochemical techniques have been developed[7,19]. It has been reported that the detection of MSI may be a promising tool for predicting treatment response for patients with stage 2 and 3 cancer, as well as ensuring a better prognosis and survival for advanced disease[20].

As MMR proteins may be in vivo heterodimerized, it has been stressed that four antibodies should be used in combination to increase specificity and sensitivity[7,21]. In our study, large surgical materials were used for cancer cases, and the total negativity of any of the antibodies was considered MSI. In cases where no staining took place, we detected negativity in one or more markers.

The main expected clinical and histopathological properties in CRC with MSI are female sex predominance, right colonic localization, poorly differentiated carcinoma morphology and the presence of intense lymphocytic infiltration[22]. In agreement with the previous literature, tumors with MSI in our study showed a female preponderance, right colonic preference, and poorly differentiated carcinoma morphology.

Proximal colon cancers have been proposed to be associated with a greater mortality rate than colon and rectum cancers[22]. It has been reported that proximal colon cancers with MSI had a better prognosis than proximal colon cancers with micro satellite stable (MSS)[22,23].

As lymph node involvement and distant metastasis status are concerned, some trials have demonstrated that tumors with MSI are associated with a lower rate of lymph node involvement than the ones with MSS[24]. In a 1250-patient CRC study, however, Mohan *et al* found a higher rate of lymphovascular and perineural invasion in stage 3 tumors with MSI than tumors with MSS[25]. As the majority of our tumors with MSI were of stage 2 or 3, we found higher lymphovascular invasion and lymph node involvement rates than the previous reports.

CONCLUSION

In CRCs with suitable clinical and histopathological properties, immunohistochemical examination incorporating the antibodies MLH1, PMS2, MSH2 and MSH6 may be an appropriate step prior to molecular analysis. It may have a decisive role for LS, family screening, and follow-up in early colorectal lesions.

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Disclaimer: None

Conflict of Interest: None

REFERENCES

1. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin 2014; 64(2):104-117.
2. Chen W, Swanson BJ, Frankel LW. Molecular genetics of microsatellite-unstable colorectal cancer for pathologist. Diagn Pathol 2017; 12(1):24.
3. Gatalica Z, Vranic S, Xiu J, Swensen J, Reddy S. High microsatellite instability (MSI-H) colorectal carcinoma: A brief review of predictive biomarkers in the era of personalized medicine. Fam Cancer 2016; 15(3):405-412.
4. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010; 138(6):2073-2087.
5. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, *et al*. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008; 26(35):5783-5788.
6. Bacher JW, Sievers CK, Albrecht MD, Grimes IC, Weiss JM, Matkowskyj KA, *et al*. Improved detection of microsatellite instability in early colorectal lesions. Plos One 2015; 10(8):e0132727.
7. Cohen R, Svrcek M, Dreyer C, Cervera P, Duval A, Pocard M, *et al*. New therapeutic opportunities based on DNA mismatch repair and BRAF status in metastatic colorectal cancer. Curr Oncol Rep 2016; 18(3):18.
8. National Comprehensive Cancer Network. Lynch Syndrome guidelines version 2.2014.
9. Funkhouser WK Jr, Lubin IM, Monzon FA, Zehnbauer BA, Evans JP, Ogino S, *et al*. Relevance, pathogenesis, and testing algorithm for mismatch repair-defective colorectal carcinomas: A report of the association for molecular pathology. J Mol Diagn 2012; 14(2):91-103.
10. Lewitowicz P,Gluszek S,Koziel D, Horecka-Lewitowicz A, Chrapek M, Wolak P, *et al*. Conventional colon adenomas harbor various disturbances in microsatellite stability and contain micro-serrated foci with microsatellite instability. PloS ONE 2017; 12(2):e0172381.
11. Yurgelun MB, Goel A, Hornick JL, Sen A, Turgeon DK, Ruffin 4th MT, *et al*. Microsatellite instability and DNA mismatch repair protein deficiency in Lynch Syndrome colorectal polyps. Cancer Prev Res (Phila) 2012; 5(4):574-582.
12. Hamilton SR, Bosman T, Boffetta P, İlyas M, Morreu H, Nakamura SI, *et al*. Tumours of the colon and rectum. Bosman T, Carneiro F, Hruban RH, Theise ND. editors. World Health Organization Classification of Tumours of the Digestive System. 4th Ed. Lyon, France: IARC Press; 2010. pp. 131-181.

13. Heitman SJ, Ronksley PE, Hilsden RJ, Manns BJ, Rostom A, Hemmelgarn BR. Prevalence of adenomas and colorectal cancer in average risk individuals: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2009; 7(12):1272-1278.
14. Ferreira AM, Westers H, Sousa S, Wu Y, Niessen RC, Olderode-Berends M, *et al*. Mononucleotide precedes dinucleotide repeat instability during colorectal tumour development in Lynch syndrome patients. J Pathol 2009; 219(1):96-102.
15. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: Current concepts and challenges. Histopath 2013; 62(3):367-386.
16. Rijcken FEM, Hollema H, Kleibeuker JH. Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. Gut 2002; 50(3):382-386.
17. Bartley AN, Hamilton SR, Alsabeh R, Ambinder EP, Berman M, Collins E, *et al*. Members of the Cancer Biomarker Reporting Workgroup, College of American Pathologists. Template for reporting results of biomarker testing of specimens from patients with carcinoma of the colon and rectum. Arch Pathol Lab Med 2014; 138(2):166-170.
18. Whitehall V, Leggett B. Microsatellite instability: Detection and management in sporadic colorectal cancer. J Gastroenterol Hepatol 2011; 26(12):1697-1699.
19. Karahan B, Argon A, Yıldırım M, Vardar E. Relationship between MLH1, MSH2, PMS, MSH6 expression and clinicopathological features in colorectal cancer. Int J Clin Exp Pathol 2015; 8(4):4044-4053.
20. Copija A, Waniczek D, Wikos A, Walkiewicz K, Nowakowska-Zajdel E. Clinical significance and prognostic relevance of microsatellite instability in sporadic colorectal cancer patients. Int J Mol Sci 2017; 18(1):107.
21. Amira AT, Mouna T, Ahlem B, Raoudha A, Majid BH, Amel H, *et al*. Immunohistochemical expression pattern of MMR protein can specifically identify patients with colorectal cancer microsatellite instability. Tumour Biol 2014; 35(7):6283-6291.
22. Phipps AI, Lindor NM, Jenkins MA, Baron JA, Win AK, Gallinger S, *et al*. Colon and rectal cancer survival by tumor location and microsatellite instability: The colon cancer family registry. Dis Colon Rectum 2013; 56(8):937-944.
23. Wray CM, Ziogas A, Hinojosa MW, Le H, Stamos MJ, Zell JA. Tumor subsite location within the colon is prognostic for survival after colon cancer diagnosis. Dis Colon Rectum 2009; 52(8):1359-1366.
24. Umeda Y, Nagasaka T, Mori Y, Sadamori H, Sun DS, Shinoura S, *et al*. Poor prognosis of KRAS or BRAF mutant colorectal liver metastasis without microsatellite instability. J Hepatobiliary Pancreat Sci 2013; 20(2):223-233.
25. Mohan HM, Ryan E, Balasubramanian I, Kennelly R, Geraghty R, Sclafani F, *et al*. Microsatellite instability is associated with reduced disease specific survival in stage III colon cancer. Eur J Surg Oncol 2016; 42(11):1680-1686.

Original Article

How does Tourniquet effect the intraocular pressure during lower extremity surgery under spinal anesthesia?

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ABSTRACT

Objective: There are many factors which may affect intraocular pressure (IOP). Tourniquet, which is used in extremity surgery, also affects IOP. There are many studies about the effect of tourniquet on IOP in patients under general anesthesia. However, there was no study about the effect of tourniquet on IOP in patients under spinal anesthesia (SA).
Design: Non-randomized prospective comparative study
Setting: Selcuk Medicine Faculty Hospital, Konya, Turkey
Subjects: Sixty American Society of Anesthesiology physical status I-II patients aged between 18-65 years planned for elective lower extremity surgery were included in the study. They were divided into Group 1 (with tourniquet) and Group 2 (without tourniquet). Exclusion criteria included chronic diseases except for controlled hypertension, known allergies to any anesthetic drugs used in the study, history of eye disease or surgery, any contraindications for spinal anesthesia and if the expected tourniquet time was longer than 120 minutes.
Intervention: Measurement of IOP
Main outcome measure: Changes in IOP at various stages of the procedure
Results: IOP decreased with SA. Tourniquet inflation increased the IOP. In both groups, IOP was lower than the baseline IOP five minutes after spinal anesthesia. However, IOP after tourniquet inflation was higher than the baseline.
Conclusion: SA decreases IOP but application of tourniquet to the lower limb increases IOP even above the baseline.

KEY WORDS: extremity, intraocular pressure, spinal anesthesia, tonometer, tourniquet

INTRODUCTION

The ocular perfusion pressure is determined by the difference between mean arterial pressure (MAP) and intraocular pressure (IOP)[1]. IOP is the product of the difference between the production and drainage of aqueous humor[2]. A decrease in MAP or increase in IOP may alter the ocular perfusion pressure. Many factors including Valsalva maneuver, breath-holding exercises, prone position, acute volume loading and positive end-expiratory pressure may increase IOP[2]. It was reported that IOP is not increased by exercise or water ingestion[3], and exercise may decrease IOP[4]. Pregnancy may effect IOP[5,6]. Most anesthetic and hypnotic agents, including inhalational anesthetics, barbiturates, opioids, neuroleptics and benzodiazepines are capable of decreasing IOP according to depth of anesthesia. It has been reported that hyperdynamic circulatory response caused by inflation of pneumatic tourniquets may contribute shift of blood into the systemic circulation as much as 500-1000 ml, known as 'tourniquet-induced hypertension'[7]. It has been reported that preoperative ipsilateral stellate ganglion block prevented tourniquet-induced hypertension during general anesthesia, and epidural blockage also prevented the physiological changes related to tourniquet inflation[8].

This prospective, non-randomized study has been planned to document if IOP changes can be prevented with spinal anaesthesia (SA) in patients who underwent lower extremity surgery with and without the pneumatic tourniquet.

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SUBJECTS AND METHODS

After approval by the Ethics Committee and written informed consent from the patients, 60 patients who are American Society of Anaesthesiologists physical status I-II, aged between 18-65 years, and posted for elective lower extremity surgery were included in the study. Patients who were planned to be operated early in the morning were selected to avoid diurnal variations in IOP. The patients were premedicated with 0.01 mg/kg midazolam intravenous before surgery. Exclusion criteria included chronic diseases except for controlled hypertension, patients who had known allergies to any anesthetic drugs used in the study, history of eye disease or surgery, any contraindications for SA and surgery time longer than 120 minutes.

Patients were not randomized. The decision to use tourniquet was made by the surgeons. The study team only observed the included patients. The tourniquet pressure was maintained at 300 mmHg in all cases. SA was given in the L4-L5 interspace using midline approach in sitting position. Local anesthetic 10 mg of hyperbaric bupivacaine (Marcaine Spinal Heavy 0.5%) and Quincke 25G spinal needle was used in all cases. Systolic pressure, diastolic pressure, MAP, peripheral oxygen saturation, sensory block level with pinprick test and IOP was recorded five minutes before spinal anesthesia (T1), five minutes after spinal anesthesia (T2), when operation started (T3) (five minutes after tourniquet inflation in tourniquet group and five minutes after T2 in group without tourniquet), and at the end of the surgery (T4). All IOP measurements were performed in a supine position, using local anesthetic proparacaine 0.5% for corneal desensitization, with Reichert Tono-Pen AVIA® Applanation Tonometer.

All data were transferred to the computer, scanned for data errors and were tabulated as percentage and standard deviation. Data were tested for the normal range. Student T-test was used for the normal ranged data and Mann Whitney U test was used for data that was outside the normal range. Categorical data were compared with Chi-square test. $P<.05$ was accepted as statistically significant.

Table 1: Demographical data and mean duration of operation in both groups

Demograghical data and operation times	Group 1 (n=30)	Group 2 (n=30)
Age (years)	40.03	39.50
Gender (female/male)	12/18	6/24
Height (cm, mean)	169	172
Weight (kg, mean)	77.80	78.87
Duration of operation (min, mean)	60.3	60.8

RESULTS

Totally, 60 participants (42 male and 18 female) have been included the study. There were 18 male and 12 female participants included in Group 1 (patients with tourniquet) whereas 24 male and 6 female participants were included in Group 2 (patients without tourniquet) (Table 1).

All observed data at various time points (T1 to T4) are shown in Tables 2 and 3. T3 IOP measurements were lower in Group 2 (16.7±2.7 mmHg) compared to Group 1 (19.1±3 mmHg) and that was statistically significant ($P<.05$).

Although mean blood loss was significantly higher in Group 2 (65±81.39 ml) compared to Group 1 (29.33±20.87 ml), there was no statistically significant difference in hemodynamic data. Measured IOP at various time points in Group 1 are shown in Table 2. Same measurements of IOP in Group 2 are shown in Table 3.

DISCUSSION

According to the results of the study, IOP decreased with SA and this is consistent with the study by Bulut *et al*, but this reduction is not statistically significant[7]. It has been observed that IOP increased with tourniquet inflation. Hunt *et al* have reported IOP rise in their study which was performed in the prone position[1]. Grosso *et al* reported transient IOP increase in the Trendelenburg position in the study, but in the next 48 hours after the operation, IOP elevation measurements had returned to normal[9]. However, to eliminate the effects of position, all measurements in our study were

Table 2: Hemodynamic parameters and IOP data in Group 1

Time	IOP	HR	SAP	DAP	MAP
T1	19.52±2.93	83.93±16.87#	134.96±13.20	81.56±11.50	100.30±12.70##
T2	18.64±2.50	78.57±13.4#	127.23±10.20	76.46±10.30	94.23±9.80##
T3	19.07±3.03	75.27±14.3#	120.53±10.90	72.96±10.90	91.33±11.50
T4	18.74±3.05	70.97±11.19#	123.73±14.00	74.90±11.30	92.57±12.15

IOP: intraocular pressure; HR: heart rate; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure
T1: five minutes before spinal anesthesia; T2: five minutes after spinal anesthesia; T3: operation start time (five minutes after tourniquet inflation in tourniquet group and five minutes after T2 in group without tourniquet); T4: end of the surgery
#HR change in T1-T3, T1-T4, T2-T4 are statistically significant ($P<.05$)
##MAP change in T1-T2 is statistically significant ($P<.05$)

Table 3: Hemodynamic parameters and IOP data in Group 2

Time	IOP	HR	SAP	DAP	MAP
T1	18.12±2.64*	86.17±10.44**	139.36±13.00	87,03±10.60	106.20±11.67***
T2	17.20±3.09	81.57±11.61**	121.36±17.00	73.06±14.70	91.13±14.66***
T3	16.77±2.68*	79.43±12.68**	117.20±14.70	70.23±11.40	87.97±12.57***
T4	17.90±2.86	73.57±10.15**	119.43±12.90	73.23±11.50	91.30±12.27***

IOP: intraocular pressure; HR: heart rate; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; MAP: mean arterial pressure
T1: five minutes before spinal anesthesia; T2: five minutes after spinal anesthesia; T3: operation start time (five minutes after tourniquet inflation in tourniquet group and five minutes after T2 in group without tourniquet); T4: end of the surgery
*IOP in T1-T3 is statistically significant (P<.05)
**HR in T1-T2, T1-T4, T2-T4, T3-T4 are statistically significant (P<.05)
***MAP in T1-T2, T1-T3, T1-T4 are statistically significant (P<.05)

carried out in a neutral supine position. It is, therefore, not possible to evaluate the effect of position on IOP in our study.

The MAP decrease of Group 1 and Group 2 in T1-T2 measurements was statistically significant. It has been thought that decrease is related to SA induced hypotension[10]. However, there was no statistically significant difference in IOP measurements of the same period, and this suggests the possibility that there is no correlation between IOP and MAP. Despite the lack of a statistically significant difference between T1-T3 measurements of MAP in Group 2, there was a statistically significant difference in IOP measurements that support this thesis. These findings contradict the data of Bulut *et al*. They have reported that there was a correlation between MAP and IOP[7]. In the study which was performed in patients under general anesthesia, it was reported that IOP is related to retinal venous pressure and IOP increases when retinal venous pressure rises. However, according to our data, we did not find any correlation between MAP and IOP, and IOP increased while MAP decreased in Group 1 after tourniquet inflation. MAP decrease was thought to be due to SA[10]. Dumskyj *et al* have shown a correlation between IOP and MAP[11]. In our study, we find this correlation in Group 2, but not in Group 1. This has been attributed to tourniquet induced sympathetic activity. In Group 2, MAP is decreased due to sympathetic block caused by SA, and this is reflected as a reduction in IOP. It has been proposed that sympathetic block during SA was attenuated by tourniquet induced sympathetic activity in Group 1. Except for these results, there was no statistically significant alteration in MAP after tourniquet inflation. This suggests that patients remain hemodynamically stable during SA. In the same period, there has been significant alterations in heart rate (HR), but MAP has not been affected. According to this observation, it may be said that there are sympathetic stimuli which affect the IOP. Therefore, IOP cannot be correlated with a single variable.

It is probable that SA decreased IOP in both groups due to sympathetic block. When T2 IOP measurements have been recorded, mean sensitive block level was thoracic 9th dermatome in Group 1 and thoracic 10th dermatome in Group 2. HR, systolic and diastolic blood pressure, and MAP have decreased in the same period. As the tourniquet was in the deflated state at this point, we can state that this IOP decrease with SA occurs directly and indirectly. This can be explained as due to decrease in sympathetic activity, decrease in systolic or diastolic blood pressure, and alterations in venous pressure.

SA can cause alterations in HR by acting on both arterial blood pressure and sympathetic blockade. In addition, tourniquet inflation may influence HR independent of SA. Our findings correlate with data of Arai *et al* in HR, who reported in their study that tourniquet-induced hypertension and activation of the sympathetic nervous system can be inhibited with epidural block[8]. This decrease in HR is observed in the T1-T3 period in Group 1. The difference between T1-T3 HR measurements is statistically significant. In conclusion, it may be said that the increases in HR caused by tourniquet inflation have been attenuated by SA.

It has been observed in IOP measurements performed after the tourniquet inflation that IOP decreased while systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and MAP increased. The HR, SAP, DAP, MAP and IOP increased in Group 2. In the study conducted by Arai *et al*, ipsilateral stellate ganglion block has been shown to decrease the sympathetic stimulation induced by tourniquet in the lower extremities[8]. In our study, hemodynamic alterations caused by tourniquet inflation have been attenuated by SA. These results lead us to conclude that IOP increase can be multifactorial, including hemodynamic parameters and sympathetic stimulation.

A blood shift of up to 1000 ml into the systemic circulation may occur with tourniquet inflation. This can cause an increase in central venous pressure and arterial blood pressure[7]. Central venous

catheterization has not been done in any of our cases as there was no clinical indication. IOP is known to increase with an increase in central venous pressure. However, this cannot be decided with our data.

Mean sensory block levels were T7 in Group 1 and T5 in Group 2 when T3 measurements were recorded. Stellate ganglion is formed by C7, C8, T1 and T2 branches. The sympathetic blockade applied by Arai *et al* via stellate ganglion block is more cephalic than sympathetic blockade induced by SA[8]. Therefore, the sympathetic block induced by SA may be insufficient to prevent IOP increase due to tourniquet inflation. However, it should be emphasized that Arai *et al* had performed their study using general anesthesia. In their study, SAP, DAP and HR were recorded, but IOP measurement was not. The SAP, DAP and HR were reported to decrease in their study. These results also support our claim regarding the correlation between IOP and SAP. In T4 measurements, SAP, DAP and MAP have increased in Group 1, while HR and IOP have decreased after tourniquet deflation. Alterations in HR and IOP are thought to be caused by blood flow that turns to the surgical area with deflation of tourniquet and decrease in sympathetic activity. SAP, DAP, MAP and IOP values increased while HR decreased in Group 2.

CONCLUSION

It has been observed that IOP decreases in patients under SA. SA inhibits the sympathetic activity induced by the tourniquet. HR, SAP, DAP and MAP have not increased after tourniquet inflation but IOP increased during lower extremity operations inflating a pneumatic tourniquet. It has been thought that this clinical outcome makes SA a better choice to prevent tourniquet induced sympathetic activity. However, SA does not have an advantage in patients with elevated IOP, who are the candidates for using pneumatic tourniquets. We believe that further studies are required to protect patients from adverse effects of elevated IOP.

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REFERENCES

1. Hunt K, Bajekal R, Calder I, Meacher R, Eliahoo J, Acheson JF. Changes in intraocular pressure in anesthetized prone patients. J Neurosurg Anesthesiol 2004; 16(4):287-290.
2. Jaén-Díaz JI, Cordero-García B, López-de-Castro F, de-Castro-Mesa C, Castilla-López-Madridejos F, Berciano-Martínez F. [Diurnal variability of intraocular pressure]. Arch Soc Esp Oftalmol 2007; 82(11):675-679. [Article in Spanish]
3. Moura MA, Rodrigues LOC, Waisberg Y, de Almeida HG, Silami-Garcia E. Effects of submaximal exercise with water ingestion on intraocular pressure in healthy human males. Braz J Med Biol Res 2002; 35(1):121-125.
4. Marcus DF, Krupin T, Podos SM, Becker B. The effect of exercise on intraocular pressure I. human beings. Invest Ophthalmol 1970; 9(10):749-752.
5. Brauner SC, Chen TC, Hutchinson BT, Chang MA, Pasquale LR, Grosskreutz CL. The course of glaucoma during pregnancy: A retrospective case series. Arch Ophthalmol 2006; 124(8):1089-1094.
6. Razeghinejad MR, Tania Tai TY, Fudemberg SJ, Katz LJ. Pregnancy and glaucoma. Surv Ophthalmol 2011; 56(4):324-335.
7. Bulut NG, Karaaslan K, Ozturan KE, Cakici H, Kocoglu H. The effects of tourniquet on intraocular pressure during knee surgery. Middle East J Anaesthesiol 2011; 21(1):93-98.
8. Arai YC, Ogata J, Matsumoto Y, Yonemura H, Kido K, Uchida T, *et al*. Preoperative stellate ganglion blockade prevents tourniquet-induced hypertension during general anesthesia. Acta Anaesthesiol Scand 2004; 48(5):613-618.
9. Grosso A, Scozzari G, Bert F, Mabilia MA, Siliquini R, Morino M. Intraocular pressure variation during colorectal laparoscopic surgery: Standard pneumoperitoneum leads to reversible elevation in intraocular pressure. Surg Endosc 2013; 27(9):3370-3376.
10. Tarkkila P, Kaukinen S. Complications during spinal anesthesia: A prospective study. Reg Anesth 1991; 16(2):101-106.
11. Dumskyj MJ, Mathias CJ, Dore CJ, Bleasdale-Barr K, Kohner EM. Postural variation in intraocular pressure in primary chronic autonomic failure. J Neurol 2002; 249(6):712-718.

Original Article

Assessment of cardiovascular functions in children with attention-deficit/hyperactivity disorder who are new users of methylphenidate

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ABSTRACT

Objectives: It was aimed to evaluate cardiovascular functions via blood pressure and electrocardiogram (ECG) of patients with attention deficit and hyperactivity disorder (ADHD) who were treated with methylphenidate.
Design: This is a descriptive and prospective study.
Settings: Necmettin Erbakan University Meram Faculty of Medicine and Konya Training and Research Hospital, Turkey
Subjects: Thirty-five patients with ADHD who were selected to be treated with methylphenidate were evaluated using ECG, heart rate (beats/minute), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) recorded before treatment, and after 1st month and 3rd month of treatment.
Interventions: Heart rate, rhythm, QRS axis, P-R interval, P dispersion, QT dispersion, QTc interval and QTc dispersion were measured on ECG.
Main outcome measures: ECG changes of patients with ADHD who were treated with methylphenidate
Results: There were no statistically significant differences in the heart rate, systolic blood pressure, diastolic blood pressure, P-R interval, P dispersion, QT dispersion and QTc dispersion between the measurements performed at baseline and at one and three months of treatment. Statistically significantly increased QRS axes were observed at baseline, and at one and three months of treatment, although this increase was not clinically significant. None of the patients had adverse cardiovascular events.
Conclusion: In conclusion, methylphenidate which is used commonly in the treatment of ADHD does not alter the heart rate, blood pressure and ECG recordings at one and three months of treatment compared to the baseline.

KEY WORDS: attention-deficit/hyperactivity disorder, electrocardiography, methylphenidate

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by persistent high levels of hyperactivity, attention deficiency and impulsive behaviour in children and adolescents. Overall, prevalence of ADHD is 3-10% in children[1]. Treatment of ADHD requires a long-term, multimodal and multidisciplinary management and is based on pharmacological and/or behavioral therapy[2]. In its pharmacological treatment, stimulant (methylphenidate) and non-stimulant (atomoxetine) agents are frequently used[3]. Although they are commonly used and effective, they can cause complications such as increased heart rate, myocardial infarction, and stroke[4].

The first choice of drugs in ADHD treatment are psychostimulant drugs. Methylphenidate is the most common psychostimulant, which has direct and indirect effects on adrenergic receptors[5]. It is a sympathomimetic agent exerting effects on the heart rate and blood pressure[6]. However, there are clinical

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reports on the risks of methylphenidate such as sudden death, and therefore, caution should be exercised in its use, particularly in children with heart disease[7].

QT dispersion is a raw and approximate measure of abnormalities in repolarization in various regions of the myocardium. The measurement of QT interval dispersion is evaluated as an electrocardiographic (ECG) marker in the analysis of ventricular repolarization abnormalities, fatal arrhythmias, and therapeutic effects of some drugs[8]. Therefore, evaluation of the cardiovascular system is critical in patients who are expected to use methylphenidate for a long period of time.

In this study, we aimed to evaluate cardiovascular functions of children with ADHD under methylphenidate treatment.

SUBJECTS AND METHODS

A written informed consent from each parent was obtained and the study protocol was approved by the Ethics Committee of Necmettin Erbakan University, Meram Faculty of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 35 patients aged between 6 and 15 years who were scheduled to use methylphenidate due to ADHD were included in the study. Patients with previous history of seizure, bipolar disorder, psychotic disorder, mental retardation, pervasive development disorder, patients using psychotropic drugs, patients with valvular, pericardial or myocardial heart disease, congenital heart disease, rhythm and conduction disturbances, patients using anti-arrhythmic or using drugs that are known to affect heart rate and/or QT interval or sympathetic-parasympathetic nervous system activity were excluded from the study. Patients with systemic disease and electrolyte abnormalities were also excluded.

ECG was performed and heart rate (bpm), systolic blood pressure (SBP) (mmHg) and diastolic blood pressure (DBP) (mmHg) were recorded before starting the treatment of patients diagnosed with ADHD, and at one and three months of methylphenidate treatment (after two hours of administering the drug). In addition, ECG and blood pressure were recorded at least two hours after taking methylphenidate for all patients. Blood pressure was measured by using a cuff size appropriate for the patient and covering 2/3 of the upper arm, after 10 minutes of resting. Blood pressure and ECG measurements were performed between 10:00 AM and 3:00 PM.

In addition, ECG was performed at rest using a standard 12-lead ECG device (Nihon Kohden Cardiofax, Japan) at 25 mm/sec speed and 10 mm/mV voltage. On ECG, heart rate, rhythm, QRS axis, P-R interval, P dispersion, QT dispersion, QTc interval, and QTc dispersion were measured manually. The Bazzet's formula ($QTc=QT/\sqrt{RR}$) was used to calculate the QTc interval. The distance between the start of the QRS complex and the end of the T wave was accepted as the QT interval. Leads where the T wave was unable to be distinguished and premature beats were excluded. When the T wave had two peaks, if the second peak was smaller than 50% of the first wave, the point where the first wave reached the isoelectric point was accepted as the end of the T wave. To calculate dispersion, measurements were performed in at least nine leads in each ECG. For each lead, using a ruler, three QT and QTc intervals were calculated and the mean of the three values were obtained. The difference between the highest and the lowest mean QT values was identified as the QT dispersion, and similarly, the difference between the highest and the lowest mean QTc values was identified as the QTc dispersion. All measurements were performed manually by a single person (F.S.) and a magnifier was used to increase accuracy.

In addition, demographic data of all patients were recorded to the patient cards by either using the patient file or through their medical history.

Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in frequency (number), % (proportion), and mean ± standard deviation. The Kolmogorov-Smirnov Z normality test was used to analyze normally distributed variables. One-way analysis of variance for repeated measures was used to analyze the repeated measurements. In the analysis of the repeated measurements among themselves, the paired-samples t-test was used for the normally distributed variables, while the Wilcoxon-signed rank test was used for the abnormally distributed variables. $P<.05$ was considered statistically significant.

RESULTS

Of the 35 patients included in the study, 23 were male and 12 were female; mean age was 9.2 years (range: 6-15 years). Demographic characteristics of the patients are summarized in Table 1.

Comparison of baseline, 1st month and 3rd month of methylphenidate treatment, ECG measurements

Table 1: Baseline characteristics of the study group

Patient Characteristics	Values (N=35)
Age (years)	9.22±2.59
Height (cm)	133±17
Weight (kg)	34.31±14.57
Gender (female/male)	12(34%) / 23(66%)

Data are expressed as mean ± SD or number and proportion.

Table 2: Comparison of baseline, 1st month and 3rd month of methylphenidate treatment electrocardiogram measurements and vital signs

Electrocardiogram measurements and vital signs	Baseline	1st month	3rd month	*P*-value
Heart rate (bpm)	91.68±12.23	90.25±12.81	92.68±11.30	.160
Systolic blood pressure (mm Hg)	110.42±6.57	111.57±6.65	109.14±6.69	.090
Diastolic blood pressure (mm Hg)	65.78±6.92	66.05±8.09	66.31±6.83	.870
QRS axis (°)	64.02±17.57	66.88±16.76*	67.08±16.70*	.041
PR interval (ms)	79.28±12.84	82.50±15.21	82.14±14.31	.394
P dispersion (ms)	31.07±11.08	27.14±9.33	28.57±9.37	.203
QT dispersion (ms)	67.14±20.88	68.57±23.75	71.42±27.21	.648
QTc interval (ms)	407.54±25.44	402.60±27.96	401.42±29.52	.487
QTc dispersion (ms)	77.62±18.40	76.17±21.79	80.28±28.22	.645

*P<.05 vs baseline

and vital signs are shown in Table 2. There was no statistically significant difference in the heart rate, SBP and DBP values between pre-treatment and at one and three months of treatment (P=.160, P=.090 and P=.870, respectively). In addition, when the dependent variables were compared within the group, no statistically significant difference in the heart rate, SBP and DBP values was found between pre-treatment and at one and three months of treatment (P=.402, P=.540, P=.211, P=.163, P=.804, P=.607, respectively). Similarly, no statistically significant difference was found in the heart rate, SBP and DBP values between the measurements performed at one and three months of treatment (P=.064, P=.749, P=.057, respectively).

However, there was a significant difference in the QRS axis values between the baseline and at one and three months of treatment (P=.041). Pre-treatment QRS axis (mean ± SD) value was 64.02±17.57°, whereas it was 66.88±16.76° at one month of treatment and 67.08±16.70° at three months of treatment. When the dependent variables were compared within the group, a statistically significant difference in the QRS axis values was found between pre-treatment and at one and three months of treatment (P=.028, P=.024, respectively). However, no statistically significant difference was detected between the QRS axis values at one and three months of treatment (P=.836).

In addition, no statistically significant difference was found between pre-treatment and 1st and 3rd months of treatment in terms of PR distance, P dispersion, QTc interval, QT dispersion, and QTc dispersion (P=.394, P=.203, P=.487, P=.648, P=.645, respectively). When the dependent variables were compared within the group, no statistically significant difference was found between the pre-treatment PR distance, P dispersion, QTc interval, QT dispersion, and QTc dispersion and at one and three months of treatment (P=.173, P=.254, P=.085, P=.240, P=.279, P=.268, P=.627, P=.396, P=.737, P=.617, respectively).

Similarly, no statistically significant difference in PR distance, P dispersion, QTc interval, QT dispersion, and QTc dispersion was found between one and three months of treatment (P=.744, P=.285, P=.787, P=.479, P=.262, respectively).

DISCUSSION

In the present study, patients who received methylphenidate for the first time for ADHD were evaluated using ECG recordings and blood pressure measurements at baseline and at one and three months of treatment. No statistically significant difference in the SBP, DBP, heart rate, PR distance, QTc interval, P dispersion, QT dispersion and QTc dispersion was found between the measurement time points, namely at baseline, and at one and three months of treatment.

ADHD is one of the most common psychiatric disorders of childhood. It is a neuropsychiatric disorder which affects the child's social and cognitive development and sets the ground for the addition of other psychiatric disorders in adolescence and adulthood[9]. Methylphenidate is a major psychostimulant drug used in the treatment of this disorder. Sympathomimetic drugs (neuroadrenergic effect) are reported to cause increased SBP, DBP and heart rate, even leading to sudden death[6,10].

Efficacy, safety and adverse effects of methylphenidate have been investigated in many studies. The majority of these studies have also investigated alterations in the heart rate and blood pressure. In children with ADHD, controversial results have been obtained in the studies which evaluate the effects of methylphenidate on cardiovascular functions through vital symptoms at a very early stage[11-14]. In two different placebo-controlled studies by Martin *et al*[12] and Findling *et al*[14], consistent with our results, no statistically significant change was found in the heart rate, SBP and DBP values following methylphenidate treatment. In two other studies evaluating the effects of methylphenidate on cardiovascular functions at a very early stage in children with ADHD, Silva *et al*[13] reported a minor increase in the heart rate, SBP and DBP values, whereas Kelly *et al*[11] found an increase in the heart rate, compared to placebo. However, it should be kept in mind that all measurements in these studies

were undertaken in the laboratory setting, which may have increased the heart rate and blood pressure.

In the study by Kratochvil *et al*[15], a total of 228 children aged between 7 and 15 years and diagnosed with ADHD received methylphenidate treatment. The heart rate and blood pressure were measured at week 10, and a statistically significant increase in the heart rate, SBP and DBP values was found in in the methylphenidate group, compared to baseline. In previous studies investigating the effects of methylphenidate on cardiovascular functions through vital signs in the early and intermediate stages in children with ADHD similar to the measurement intervals in our study, methylphenidate was shown to have no effect on heart rate, SBP and DBP, compared to the baseline values, consistent with our results[16-22]. However, in a study where the blood pressure measurements were performed at time points similar to the measurement time points in the present study, in the measurements at week 12 of methylphenidate treatment, SBP and DBP values statistically significantly increased, compared to the baseline values[23].

In studies where the effects of methylphenidate on cardiovascular functions were evaluated through vital symptoms in the long term in children with ADHD, Gadow *et al*[24] reported no clinically significant changes in the heart rate, SBP and DBP values, whereas two other studies by Wilens *et al*[16,25] reported controversial results.

In the previous studies with a different design, where different treatment doses of methylphenidate was evaluated in a time period ranging from the very early stage after treatment up to two years after treatment, the heart rate and blood pressure values were evaluated within a long time period, and the results of our study are consistent with these findings[12-16]. Although there are some studies in which the heart rate and blood pressure values statistically increased, in the majority of these studies, no clinically significant increase was reported.

Although there is a limited amount of data on the rhythm in the ECG evaluation among children and adolescents with ADHD, in a prospective and observational study conducted by Arcieri *et al*[26] in children and adolescents with ADHD using methylphenidate and atomoxetine, sinus bradycardia, sinus tachycardia, right bundle branch block, and first-degree atrioventricular block in the patient group using methylphenidate were reported. However, other studies on this subject did not provide any information about rhythm. In our study, no rhythm changes or heart block were observed in the ECG at one and three months of methylphenidate treatment.

Similarly, in the studies including children and adolescents with ADHD, there is insufficient data on the PR distance. Although Arcieri *et al*[26] reported cases where the PR interval increased, no comparisons between the pre-treatment and post-treatment PR interval values were performed. In another study in children using methylphenidate due to ADHD, changes in the ECG were evaluated at six weeks and six months of treatment, no statistically and clinically significant changes were detected in the P-R and QTc interval, consistent with our study results[27]. However, the difference of this study from the present study and many other studies is that a rather higher dose of methylphenidate was used. Despite these high doses, there were still no changes in the P-R and QTc interval. Contrary to these results, in one of the two different studies by Ari *et al*, there was a statistically significant increase in QTc interval compared to the baseline; however, the increased interval was not suggestive of any pathology in any of the patients[28,29]. On the other hand, in the other study by Ari *et al*, no statistical or clinical changes were reported in the QTc interval, compared to the baseline[29]. In studies evaluating the effect of methylphenidate on QTc interval in children with ADHD, similar results were obtained, consistent with our findings[15,30].

QT dispersion is modulated by the central nervous system and represents heterogeneity in myocardial repolarization. Various clinical studies have shown that increased QT dispersion increases the risk of serious ventricular arrhythmia and sudden death[31]. Lengthened QT interval decreases the ventricular fibrillation threshold and increases the risk of sudden death. It is important to assess the effect of methylphenidate on these various ECG parameters due to its sympathomimetic effect and long term use. However, both the studies and literature on this subject are limited.

Similarly, in one of the two studies where ECG measurements two hours after methylphenidate use were evaluated, there was no statistically significant change in the QT dispersion[32]. However, in the other study, both QT dispersion and QTc dispersion significantly decreased following the treatment[33].

In our study, consistent with the limited literature data, there were no significant statistical and clinical changes in the QTc interval, QT dispersion and QTc dispersion between the baseline and at one and three months of methylphenidate treatment. In addition, P dispersion, which was not analyzed previously in patients with ADHD receiving methylphenidate, was evaluated in our study. P dispersion was reported to increase in different clinical conditions, which might lead to atrial fibrillation[34]. In our study, however, no statistically or clinically significant changes in the P dispersion were found at one and three months of methylphenidate treatment, compared to baseline.

Similarly, in several studies including patients with ADHD receiving methylphenidate, we were unable to obtain any data on the QRS axis. In our study, although there was a statistically significant increase in the QRS axis values at one and three months of treatment compared to baseline, this increase was not clinically significant.

Although rare, serious cardiovascular complications were reported in children with ADHD receiving methylphenidate. In the study by Fernandez *et al*[35], three of 720 patients had serious cardiovascular complications, one being supraventricular tachycardia and the other two being hypertension accompanied by sinus tachycardia. However, it was stated by the authors that there were no abnormal findings regarding the increase of QTc interval or QT/QTc ratio. Other than the reported complications, there are also pediatric cases in the literature on methylphenidate overdose. In the case reports of two girls who used a high dose of methylphenidate for suicide, no cardiovascular abnormalities other than mild hypertension and sinus tachycardia were reported[36]. In our study, none of the patients had any complications throughout the study.

CONCLUSION

In conclusion, we believe that methylphenidate, which is widely used in ADHD treatment, can be used safely without any change or abnormalities in vital signs and ECG findings.

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: A systematic review and metaregression analysis. Am J Psychiatry 2007; 164(6):942-948.
2. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2007; 46(7):894-921.
3. Cheng JY, Chen RY, Ko JS, Ng EM. Efficacy and safety of atomoxetine for attention-deficit hyperactivity disorder in children and adolescents – meta-analysis and meta-regression analysis. Psychopharmacol 2007; 194(2):197-209.
4. Gelperin K, Brinker AD, Avigan MI. MedWatch reporting of death, sudden death, and cardiovascular events in association with stimulant used in the treatment of ADHD over a recent 5-years period. Available at www.cfsan.fda.gov/*frf/forum06/1-04.htm. Accessed July 3, 2006.
5. Safer DJ, Zito JM, Fine EM. Increased methylphenidate usage for attention deficit disorder in the 1990s. Pediatrics 1996; 98(6 Pt 1):1084-1088.
6. Volkow ND, Wang GJ, Fowler JS, Molina PE, Logan J, Gatley SJ, *et al*. Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. Psychopharmacol (Berl) 2003; 166(3):264-270.
7. Nissen SE. ADHD drugs and cardiovascular risk. N Engl J Med 2006; 354:1445-1448.
8. Etheridge SP, Shaddy RE. QT dispersion after beta-blocker therapy in children with heart failure. Am J Cardiol 2003; 91(12):1497-1500, A8.
9. Tannock R. Attention deficit hyperactivity disorder: Advances in cognitive, neurobiological, and genetic research. J Child Psychol Psychiatry 1998; 39(1):65-99.
10. Rapport MD, Moffitt C. Attention deficit/hyperactivity disorder and methylphenidate. A review of height/weight, cardiovascular, and somatic complaint side effects. Clin Psychol Rev 2002; 22(8):1107-1131.
11. Kelly KL, Rapport MD, DuPaul GJ. Attention deficit disorder and methylphenidate: A multi-step analysis of dose-response effects on children's cardiovascular functioning. Int Clin Psychopharmacol 1988; 3(2):167-181.
12. Martin CA, Guenthner G, Bingcang C, Rayens MK, Kelly TH. Measurement of the subjective effects of methylphenidate in 11- to 15-year-old children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2007; 17(1):63-73.
13. Silva R, Muniz R, Pestreich LK, Brams M, Childress A, Lopez FA. Efficacy of two long-acting methylphenidate formulations in children with attention- deficit/hyperactivity disorder in a laboratory classroom setting. J Child Adolesc Psychopharmacol 2005; 15(4):637-654.
14. Findling RL, Short EJ, Manos MJ. Short-term cardiovascular effects of methylphenidate and adderall. J Am Acad Child Adolesc Psychiatry 2001; 40(5):525-529.
15. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, *et al*. Atomoxetine and methylphenidate treatment in children with ADHD: A prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry 2002; 41(7):776-784.
16. Wilens TE, McBurnett K, Bukstein O, McGough J, Greenhill L, Lerner M, *et al*. Multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2006; 160(1):82-90.
17. McGough JJ, McBurnett K, Bukstein O, Wilens TE, Greenhill L, Lerner M, *et al*. Once-daily OROS methylphenidate is safe and well tolerated in adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2006; 16(3):351-356.
18. Greenhill LL, Findling RL, Swanson JM, ADHD Study Group. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics 2002; 109(3):E39.
19. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, *et al*. Randomized, controlled trial of oros methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics 2001; 108(4):883-892.

20. Findling RL, Short EJ, McNamara NK, Demeter CA, Stansbrey RJ, Gracious BL, *et al*. Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention- deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2007; 46(11):1445-1453.
21. Findling RL, Quinn D, Hatch SJ, Cameron SJ, DeCory HH, McDowell M. Comparison of the clinical efficacy of twice-daily Ritalin and once-daily Equasym XL with placebo in children with Attention Deficit/ Hyperactivity Disorder. Eur Child Adolesc Psychiatry 2006; 15(8):450-459.
22. Gau SS, Shen HY, Soong WT, Gau CS. An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. J Child Adolesc Psychopharmacol 2006; 16(4):441-455.
23. Yildiz O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and methylphenidate treatment in children with ADHD: The efficacy, tolerability and effects on executive functions. Child Psychiatry Hum Dev 2011; 42(3):257-269.
24. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Grossman S. Long-term methylphenidate therapy in children with comorbid attention-deficit hyperactivity disorder and chronic multiple tic disorder. Arch Gen Psychiatry 1999; 56(4):330-336.
25. Wilens TE, Biederman J, Lerner M; Concerta Study Group. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: Results from a one-year follow-up study. J Clin Psychopharmacol 2004; 24(1):36-41.
26. Arcieri R, Germinario EA, Bonati M, Masi G, Zuddas A, Vella S, *et al*; Italian Attention-Deficit/Hyperactivity Disorder Regional Reference Centers. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. J Child Adolesc Psychopharmacol 2012; 22(6):423-431.
27. Hammerness P, Wilens T, Mick E, Spencer T, Doyle R, McCreary M, *et al*. Cardiovascular effects of longer-term, high-dose OROS methylphenidate in adolescents with attention deficit hyperactivity disorder. J Pediatr 2009; 155(1):84-89.
28. Ari ME, Cetin II, Ekici F, Kocabas A, Eminoglu S, Guney E, *et al*. The assessment of early cardiovascular alterations due to the use of methylphenidate in patients with attention deficit and hyperactivity disorder. Turkish J Pediatr Dis 2013; 3:119-123.
29. Ari ME, Cetin II, Ekici F, Kocabas A, Eminoglu S, Guney E, *et al*. Assessment of cardiovascular risks due to methylphenidate in six months of treatment in children with attention deficit and hyperactivity disorder. Bulletin of Clinical Psychopharmacology 2014; 24(3):248-252.
30. Nahshoni E, Sclarovsky S, Spitzer S, Zalsman G, Strasberg B, Weizman A. Early repolarization in young children with attention-deficit/hyperactivity disorder versus normal controls: A retrospective preliminary chart review study. J Child Adolesc Psychopharmacol 2009; 19(6):731-735.
31. Paventi S, Bevilacqua U, Parafati MA, Di Luzio E, Rossi F, Pelliccioni PR. QT dispersion and early arrhythmic risk during acute myocardial infarction. Angiology 1999; 50(3):209-215.
32. Lamberti M, Italiano D, Guerriero L, D'Amico G, Siracusano R, Ingrassia M, *et al*. Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with attention-deficit hyperactivity disorder. Neuropsychiatr Dis Treat 2015; 11:1169-1174.
33. Ilgenli TF, Congologlu A, Ozturk C, Turkbay T, Akpinar O, Kilicaslan F. Acute effect of methylphenidate on QT interval duration and dispersion in children with attention deficit hyperactivity disorder. Adv Ther 2007; 24(1):182-188.
34. Aytemir K, Ozer N, Atalar E, Sade E, Aksoyek S, Ovunc K, *et al*. P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 2000; 23(7):1109-1112.
35. Fernández-Fernández MA, Rufo-Campos M, Mateos-Checa R, Munoz-Cabello B, Madruga-Garrido M, Blanco-Martinez B. [Cardiovascular side effects secondary to treatment with methylphenidate]. Rev Neurol 2010; 50(9):573-574. [Article in Spanish]
36. McCarthy S, Cranswick N, Potts L, Taylor E, Wong ICK. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: A retrospective cohort study of children, adolescents and young adults using the General Practice Research Database. Drug Saf 2009; 32(11):1089-1096.

Original Article

A six-year descriptive-analytical study of Pediculosis Capitis in the Southwestern Iran

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ABSTRACT

Objectives: This study aimed to determine the prevalence of head pediculosis among school children in urban and rural areas of Eastern Ahvaz, southwestern Iran, during 2008 to 2013.
Design: Descriptive-analytical study
Setting: School of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
Subjects: Totally 5730 pupils from elementary, middle and high schools were randomly selected by multistep method.
Intervention: Data was collected through school screening programs by trained persons using a questionnaire that included the information on the diagnostic result of head lice. The screening method was by inspection. The results and demographic data were analyzed by SPSS software.
Main outcome measure: We considered the following demographic and epidemiological parameters: age, gender, educational level, history of infestation, season and geographical area.
Results: The infestation of head lice was 5730 cases. Of those affected with pediculosis, 75.6% lived in villages and 24.4% were rural residents. Most of the patients were found in the autumn (60%). Overall, 79.6% of students with pediculosis studied in primary schools, and 17.9% of those infested with pediculosis had a previous history of this infestation. The prevalence of pediculosis was higher in females than in males (97.2% vs. 2.8%, respectively).
Conclusion: Our results on the higher prevalence of head pediculosis in females than in males are in line with many previous researches. Meanwhile, the rate of infested children was different according to the age groups. These differences might be associated with behavioral variations in different genders and age groups.

KEY WORDS: epidemiology, head lice, Iran, prevalence

INTRODUCTION

Lice are wingless arthropods that feed on human blood and can infest head, body and pubic hair. Nits are white, hard, oval lice eggs that attach to the hair shaft at a 1-1.15 cm distance from the scalp and hatch within 8-10 days after they are laid[1]. Head lice infestation is known as Pediculosis capitis and is considered a highly contagious condition[2].

Today, due to improved living standards, especially in wealthy communities, body lice infestation has become less common; however, head lice infestation cases are still being reported in almost all parts of the world. Despite their widespread occurrence throughout the world, head lice are often reported in temperate regions and can cause annoyance to humans, which is comparable to that caused by mosquitoes in tropical regions[3].

Head lice can spread by direct contact with the hair of an infested person and sharing of personal items, such as hats, combs, scarves, underclothes, towels, and even mobile phones. Yet, head-to-head contact with someone already infested is the most common way to get head lice[4]. Head lice infestation is more prevalent in poorer areas with high population density, where there is lack of personal hygiene and health facilities[5,6]. Previous studies showed that head lice infestation is more prevalent in rural areas than in urban ones[7]. During the day, lice suck the hosts' blood several times and with each bite, inject their salivary proteins into their bodies. Their bites can cause allergic

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reactions, fatigue, insomnia, skin lesions, discomfort and irritation in victims. In some cases, acute allergic reactions, such as intense itching, occur after several consequent lice salivary protein injections[8].

In developed countries, the prevalence rate of head lice infestation among elementary school children is estimated to be 2-10 percent. In the United States, 6-12 million people are diagnosed with lice infestation each year, resulting in $367 million being annually spent on lice infestation control and treatment programs[9]. According to the findings of a study conducted in France, 17% of pupils were infested with head lice[10]. Head lice infestation is prevalent in all parts of the world, including Iran. It is especially more prevalent in poor areas with high population density and lack of personal hygiene, and has a relatively high prevalence rate in rural areas, especially among children[11]. In some parts of Iran, the prevalence rate of head lice infestation is reported to be 6-30%[12]. Unfortunately, different factors, including excessive population growth, urbanization, the villagers' migration to the cities, marginality and establishment of satellite towns with minimum health and welfare facilities have contributed to the emergence and prevalence of head lice infestation and other communicable diseases in such areas[11]. Given its hot and arid climate and high population density, Ahvaz County (southwestern Iran) is considered a favorable environment for lice population growth. The present study aimed at estimating the prevalence rate of head lice infestation among school students in the eastern area of Ahvaz, identifying some of the risk factors along with their role and impact probability, and providing health officials with appropriate plans and solutions to control this health problem in this region.

SUBJECTS AND METHODS

Ahvaz is a county with a hot and arid climate located at the center of Khuzestan Province. The statistical population of this descriptive study consisted of all pupils going to schools located in eastern Ahvaz. These school students were examined for lice infestation between 2008 and 2013. Upon obtaining the required authorizations and coordinating with the Health Office at Ahvaz Department of Education and Ahvaz Health Network, all the students with suspected head lice infestation were examined and identified. The process was done with the help of school health educators. Accordingly, standard questionnaires were used to record some demographic and epidemiologic characteristics of students diagnosed with lice infestation. Data such as grade level, gender, place of residence, *etc.* were collected and each student diagnosed with lice infestation was separately interviewed. In all suspected cases of infestation, head hair on the back of the neck and around the ears was examined with a hand lens and a fine-tooth comb for 2-3 minutes, looking for live lice and nits. It should be noted that diagnosis of active lice infestation was based on the available standard (Texas Guide to School Health Services) and confirmed upon finding the parasite at any of its developmental stages or the egg at a 1/4 inch distance from the scalp. In addition, inactive head lice infestation was confirmed in cases where lice eggs were found at intervals more than 1/4 inch from the scalp and no lice were observed even after combing the hair. Informed consent was obtained from the respondents. They were made to understand that participation is voluntary and there was no consequence for non-participation. The college research review committee revised the paper according to the rule and regulation. Accordingly, the study was approved by the Ethics Committees of Ahvaz Jundishapur University of Medical Sciences. Eastern Ahvaz Health Services Center and the Educational office administrative authorities at district level were informed about the study and their consent was obtained with the letter. All information obtained was kept confidential. The descriptive statistics, including frequency distribution and percentage were used to analyse the data. The analysis was performed using SPSS version 18. For all analyses, $P<.05$ was taken as significant.

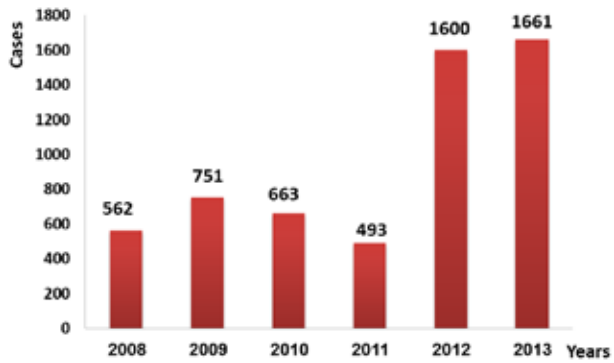

Fig 1: Frequency distribution of head lice infestation by year in the eastern area of Ahvaz, Southwestern Iran (2008-2013)

RESULTS

The present study was aimed at epidemiologically investigating head lice infestation among students going to schools located in eastern Ahvaz. Accordingly, students diagnosed with head lice infestation were studied based on different parameters, including gender, place of residence, grade level, *etc.* The present study was conducted on a total of 462,431 students studying at different grade levels in schools located in eastern Ahvaz from the academic years of 2008 to 2013. From among these students, 5730 (1.2%) were definitely diagnosed with head lice infestation. During the aforementioned period, the frequency of head lice

Table 1: Frequency distribution of head lice infestation in school pupils by sex, geographical area and educational level in the eastern area of Ahvaz, Southwestern Iran (2008-2013)

Year	Infested /Examined No. (%)	Sex		Geographical area		Educational level		
		Male Infested /Examined No. (%)	Female Infested /Examined No. (%)	Rural Infested /Examined No. (%)	Urban Infested /Examined No. (%)	Primary Infested/ Examined No. (%)	Middle Infested/ Examined No. (%)	High Infested/ Examined No. (%)
2008	562/88200 (0.6)	19/31765 (0.1)	543/56435 (0.9)	152/21098 (0.7)	410/67102 (0.6)	504/41392 (1.2)	41/26244 (0.2)	17/20564 (0.1)
2009	751/63618 (1.2)	21/20351 (0.1)	730/43267 (1.7)	201/9387 (2.1)	550/542312 (1.0)	621/30762 (2.0)	68/19865 (0.3)	62/12991 (0.5)
2010	663/74921 (0.9)	3/30316 (0.01)	660/44785 (1.5)	73/15423 (0.5)	590/59498 (0.9)	528/35721 (1.5)	73/20357 (0.4)	62/18843 (0.3)
2011	493/78546 (0.6)	33/34720 (0.1)	460/43826 (1.1)	413/17872 (2.3)	80/60674 (0.1)	172/40726 (0.4)	212/21938 (1.0)	109/15882 (0.7)
2012	1600/90439 (1.8)	47/24876 (0.2)	1553/65563 (2.4)	480/24072 (2.0)	1120/66367 (1.7)	1368/63133 (2.1)	167/16039 (1.0)	65/11267 (0.6)
2013	1661/66707 (2.5)	37/17368 (0.2)	1624/49321 (3.3)	77/2560 (3.0)	1584/64117 (2.5)	1368/41174 (3.3)	122/12005 (1.0)	171/13528 (1.3)
Total	5730/462431 (1.2)	160/159234 (0.1)	5570/303197 (1.8)	1396/90412 (1.5)	4334/372019 (1.2)	4561/252908 (1.8)	683/116448 (0.6)	486/93075 (0.5)

infestation had an increasing and decreasing trend. In other words, in the first academic year (2008-2009), 562 (0.6%) students were diagnosed with head lice infestation, while, in the second, third, fourth and fifth academic years, the number was 751 (1.2%), 663 (0.9%), 493 (0.6%) and 1600 (1.8%), respectively. In the final academic year, the number of students diagnosed with head lice infestation was 1661 (2.5%, Figure 1).

According to the results concerning the gender variable, from among the 303,197 female students, 5570 were diagnosed with pediculosis, while out of 159,234 male students, 160 were diagnosed with the same condition. Thus, from among the 5730 infested students, 5570 were female and 160 were male. In other words, the frequency was 97.2% among female students and 2.8% among male students. The statistical analysis showed that the frequency of head lice infestation was significantly different in the two gender groups in the aforementioned period. During all the academic years, the prevalence of head lice infestation was significantly higher in female students than in their male counterparts (Table 1).

In order to investigate the effect of place of residence on the prevalence of head lice infestation, the students were categorized based on their place of residence. From among the examined students, 372,019 students lived in urban areas, 4334 of which were diagnosed with head lice infestation. Thus, the prevalence rate of head lice infestation in urban areas was 1.2%. From the remaining 90,412 students who were rural residents, 1396 subjects were diagnosed with the same condition, indicating a prevalence rate of 1.5%. Thus, out of 5730 diagnosed cases, 75.6% lived in the urban areas and 24.4% were rural residents (Table 1).

In order to study the relationship between grade level and prevalence of head lice infestation, students were categorized into three groups, namely, elementary school students, junior high school students, and senior high school students. According to Table 1, the overall head lice infestation prevalence rate among elementary students, junior high school students and senior high school students was 1.8%, 0.6% and 0.5%, respectively. From among 5730 students diagnosed with head lice infestation, 4561 (79.6%) were elementary students,

Table 2: Frequency distribution of head lice infestation in school pupils by infestation history and season in the eastern area of Ahvaz, Southwestern Iran (2008-2013)

Year	Infestation History		Seasons		
	Yes No. (%)	No No. (%)	Spring Infested/Examined No. (%)	Autumn Infested/Examined No. (%)	Winter Infested/Examined No. (%)
2008	62 (11.0)	500 (89.0)	8/987 (0.8)	362/43785 (0.8)	192/40428 (0.5)
2009	101 (13.4)	650 (86.6)	5/1020 (0.5)	443/31792 (1.4)	303/30806 (1.0)
2010	70 (9.7)	651(90.3)	10/1090 (0.9)	332/52095 (0.6)	321/19736 (1.6)
2011	210 (20.7)	806 (79.3)	19/4712 (0.4)	531/41860 (1.3)	424/28974 (1.5)
2012	305 (23.1)	1014 (76.9)	19/4712 (0.4)	724/45765 (1.6)	576/42439 (1.4)
2013	280 (20.6)	1081(79.4)	34/9571 (0.4)	1045/39939 (2.6)	382/22720 (1.7)
Total	1028 (17.9)	4702 (82.1)	95/22092 (0.4)	3437/255236 (1.3)	2198/185103 (1.2)

683 (11.9%) went to junior high school, and 486 (8.5%) attended senior high school.

The prevalence rate of head lice infestation was highest in autumn months. Seasonal distribution of head lice infestation prevalence showed that 3437 (60%), 2198 (38.3%), and 95 (1.7%) cases were reported in autumn, winter and spring, respectively (Table 2).

From among the patients diagnosed with head lice infestation, 4702 (82.1%) cases did not have any previous history of head lice infestation, while 1028 (17.9%) had a previous history of the condition (Table 2).

DISCUSSION

Head lice are ectoparasites that can infest anyone regardless of age, gender and socioeconomic status. Schools are one of the main environments where head lice infestation is prevalent. During the six academic years in question, the frequency of head lice infestation among students going to schools located in eastern Ahvaz had an increasing and decreasing trend. The average head lice infestation prevalence rate among these students was 1.23%. According to a similar study by Modarresi, the prevalence rate of head lice infestation among school students in the city of Tonekabon (Mazandaran Province) was 5.74%[13]. In other studies conducted in elementary schools in the cities of Zabol (Sistan - Baluchestan Province), Sanandaj (Kurdistan Province), and Aran va Bidgol (Isfahan Province), the prevalence rate of head lice infestation was reported as 29.4%[14], 7.7%[15] and 0.47%[16], respectively. Several epidemiologic studies conducted at schools in different countries showed that the prevalence rate of head lice infestation in France, South Korea, Australia, Spain, Taiwan, Libya, Lebanon, Northern Jordan, UK, Tanzania and China were 15%, 37.2%, 33.7%, 3.39%, 40%, 87.6%, 8%, 13.4%, 28.3%, 5.3% and 12.8%, respectively[17-26]. Head lice infestation is more prevalent among people belonging to social classes with lower economic and cultural resources, and less access to health facilities. The high prevalence rate of infestation in some regions might also be attributed to factors such as harsh geographic and climatic conditions. For instance, it has been shown that head lice infestation is more prevalent in tropical regions[12].

As head lice infestation is mainly spread by direct contact, children can get infested while playing with each other (due to frequent head-to-head contact) or sharing personal items, such as scarves, combs, and hats. At the same time, the higher prevalence of infestation among female students might seemingly be attributed to the behaviors more common among female students which result in longer close physical contact between them[12]. In this study, the prevalence of head lice infestation was higher in female students than in males. Other studies conducted in Iran revealed that the prevalence rate of head lice infestation among elementary students in Shahr-e Qods County (Tehran Province) and Abadeh County (Fars Province) were 2.3% and 0.06%, respectively. In Shahr-e Qods, the infestation prevalence rate among female and male students was 3.3% and 1.3% respectively[27]. In Abadeh, although prevalence rate among female students was 0.12%, none of the male students were diagnosed with the condition[28]. In Shemiranat County (Tehran Province), head lice infestation was reported to be more prevalent among female students than among their male counterparts[29]. In Qazvin County (Qazvin Province), head lice infestation prevalence rate among elementary students was estimated as 1.1% and higher among female students[30].

Head lice infestation was more prevalent in autumn. Late autumn weather conditions characterized by regular heavy rainfalls create a fertile ground for the growth and development of several insects including lice. This will significantly contribute to the widespread and intensified prevalence of the infestation within the population. Moreover, in humid and relatively cold weather conditions, most people wear warm cloths and prefer to remain indoors. This is particularly true for school students as they leave their warm clothes on benches or coat racks, which will eventually spread the infestation. Thus, given the previously mentioned points and the favorable conditions for both direct and indirect (through clothes and beddings) head lice transmission, high head lice infestation prevalence rate among students and their families can be attributed to students' tendency to leave and stack unwanted clothes on benches, coat racks or swimming pool lockers in schools and to share personal items with family members.

There was also a significant relationship between the current head lice infestation and any previous history of the same infestation. Lice eggs might have remained in the victim's hair from some previous infestation, or some family members or acquaintances might have acted as the infestation source, needing mass treatment. Additionally, some unhealthy behaviors leading to the previous infestation might still be present and have caused re-infestation. These behaviors could belong to the victims themselves or their family members or acquaintances. This finding confirmed the results of two separate studies conducted by Rafinejad and Farzinnia in Amlash County (Gilan Province) and Qom County (Qom Province), respectively[3,31].

CONCLUSION

Given the significant role of school health educators in increasing students' awareness and performing regular examinations on them, it is recommended that appropriate measures be taken to supply schools with

health educators. In cases where there is no possibility of supplying schools with health educators, in-service training programs can be organized for school teachers so that they are able to diagnose the infestation in students and proceed with timely treatment measures, in order to prevent the spread of infestation. Regular hair-combing as well as hair-washing with warm water and soap reduces the number of nymphs and adult lice infesting the hair. However, these measures are not helpful in eliminating head lice eggs attached to the hair shafts. Thus, metal or plastic fine-tooth combs should be used to remove both lice and nits attached to the hair shafts. Additionally, school health educators should be equipped with louse detector combs. Raising public awareness is another effective measure in preventing head lice infestation in different communities. As a result, by educating students on personal hygiene, school health educators can play a significant role in fighting this highly contagious health problem.

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REFERENCES

1. Habif TP. Infestations and Bites. In: Clinical Dermatology, 4th ed. Philadelphia, Pennsylvania: Mosby, Inc, 2006: 352-355.
2. Zabihi A, Jafarianamiry S, Rezvani S, Bizhani A. Epidemiology of head lice infestation in primary school children at Babol in 2003. J Babol Univ Med Sci 2005; 28:88-93. [In Persian].
3. Farzinnia B, Hanafi-Bojd AA, Raieskarami SR, Jafari T. Epidemiology of Pediculosis Capitis in Female Primary School Pupils Qom. Hormozgan Med J 2004; 8(2):103-108. [In Persian].
4. Davarpanah MA, Rasekhi Kazerouni A, Rahmati H, Neirami R, Bakhtiary H, Sadeghi M. The prevalence of pediculus capitis among the middle school children in Fars province, southern Iran. Caspian J Intern Med 2013; 4(1):607-610.
5. Alempour-Salemi J, Shayeghi M, Zeraati H, Akbarzadeh K, Basseri H, Ebrahimi B, *et al*. Some aspects of head lice infestation in Iranshahr area (Southeast of Iran). Iranian J of Pub Health 2003; 32(3):60-63.
6. Omidi A, Khodaveisi M, Moghimbeigi A, Mohammadi N, Amini R. Pediculosis Capitis and relevant factors in secondary school students of Hamadan, West of Iran. J Res Health Sci 2013; 13(2):176-180.
7. Borges R, Mendes J. Epidemiological aspects of head lice in children attending day care centres, urban and rural schools in Uberlandia, central Brazil. Mem Inst Oswaldo Cruz 2002; 97(2):189-192.
8. Moradi A, Bathaii SJ, Shojaeian M, Neshani A, Rahimi M, Mostafavi E. Outbreak of pediculosis capitis in students of Bahar in Hamedan province. Journal of Dermatology and Cosmetic 2012; 3(1):26-32.
9. Canyon DV, Speare R, Muller R. Spatial and kinetic factors for the transfer of head lice (Pediculus capitis) between hairs. J Invest Dermatol 2002; 119(3):629-631.
10. Courtiade C, Labreze C, Fontan I, Taieb A, Maleville J. [*Pediculosis capitis*: a questionnaire survey in 4 schools of the Bordeaux Academy, 1990-1991]. Ann Dermatol Venereol. 1993; 120(5):363-368. [Article in French]
11. Razavi M. Epidemiology of pediculus humanus capitis infestation and effective factors in elementary schools of girls, villages of Islam Abad district in Tehran city. 2nd Congress of Parasites diseases in Iran. 1995.
12. Rafie A, Kasiri H, Mohammadi Z, Haghighizade M. [Pediculosis capitis and its associated factors in girl primary school children in Ahvaz City in 2005-2006]. Iran J Infect Dis Trop Med 2009; 45:41-45. [In Persian].
13. Modarresi M, Mansoori Ghiasi MAN, Modarresi M, Marefat A. The prevalence of head lice infestation among primary school children in Tonekabon, Iran. Iran J Infect Dis Trop Med 2013; 18(60):41-45.
14. Abbas-zadeh M, Masinaee-Nejad N, Dabirzadeh M, Heidari M. [Epidemiology of head lice infestation among girl primary school children in Zabol (2003)]. The journal of Toloo - e -behdasht 2004; 3:10-15. [In Persian].
15. Yaghmaie R, Rad F, Ghaderi A. Prevalence of head lice infestation in girl primary school children in Sanandaj in 2004. Iranian J Infect Dis Trop Med 2006; 12:71-74.
16. Doroudgar A, Sadr F, Sayah M, Doroudgar M, Tashakor Z, Doroudgar M. [Prevalence and associated factors of head lice infestation among primary schoolchildren in city of Aran and Bidgol (Esfahan Province, Iran)]. Payesh 2011; 10:439-447. [In Persian].
17. Combescot C. [Current epidemiology of pediculosis capitis]. Bull Acad Natl Med 1990; 174(2):231-236. [Article in French]
18. Huh S, Pai KS, Lee SJ, Kim KJ, Kim NH. Prevalence of head louse infestation in primary school children in Kangwon-do, Korea. Korean J Parasitol 1993; 31(1):67-69.
19. Speare R, Buettner PG. Head lice in pupils of primary school in Australia and implications for control. Int J Dermatol 1999; 38(4):285-290.
20. Magra Sáenz de Buruaga G, Goiria Ormazabal JI, López Martínez I, Pérez Rodrigo C, Bonet Romero T, Caturla Latorre J. [Pediculosis capitis: Epidemiologic study of 23624 school children in Bilbao]. Rev Sanid Hig Publica (Madr) 1989; 63(1-2):49-62. [Article in Spanish]

21. Fan PC, Chao D, Lee KM, Chan CH, Liu HY. Chemotherapy of head louse (*Peidculus humanas capitis*) infestation gamma benzene hexachloride (gamma-BHC) among school children in Szu-Hu district, Yunlin country, Central West Taiwan. Zhonghua Yi Xue Za Zhi (Taipei) 1991; 48(1):13-19.
22. Saab BR, Shararah N, Makarem M, Sarru E, Usta J, Khogali M. Data from a public school health project in Beirut. J Med Liban 1996; 44(2):63-67.
23. Amr ZS, Nusier MN. Pediculosis capitis in northern Jordan. Int J Dermatol 2000; 39(12):919-921.
24. Downs AM, Stafford KA, Stewart GH, Coles GC. Factors that may be influencing the prevalence of head lice in British school children. Pediatr Dermatol 2000; 17(1):72-74.
25. Henderson CA. Skin disease in rural Tanzania. Int J Dermatol 1996; 35(9):640-642.
26. Fan CK, Liao CW, Wu MS, Hu NY, Su KE. Prevalence of Pediculus capitis infestation among school children of Chinese refugees residing in mountanous areas of northern Thailand. Kaohsiung J Med Sci 2004; 20(4):183-187.
27. Zndavr H, Ormazdi H, Akhlaghi L, Razmjo E, Memar AR, Ramtane Hadiqi R, *et al*. Prevalence of pediculosis capitis , pediculus humanus and its associated factors in primary school students in the Qods City , Tehran Province in the academic year of 2007-2008. Articles abstract book of the sixth national conference and the first regional congress of Parasitology and parasitic diseases, Razi Vaccine and Serum Research Institute, Karaj, 2008. [In Persian].
28. Hassan Zadeh J, Ahmadi A. Prevalence of pediculosis [head lice] and its associated factors in primary school students in the Abadeh city in Fars province in the academic year 2007-2008. Articles abstract book of the sixth national conference and the first regional congress of Parasitology and parasitic diseases, Razi Vaccine and Serum Research Institute, Karaj, 2008. [In Persian].
29. Yusophi AR, Keighobadi M, Aminpour A. Prevalence of pediculosis infection in the referred patients to the Shemiranat city health center in Tehran during the years 2002-2006. Articles abstract book of the sixth national conference and the first regionalcongress of Parasitology and parasitic diseases, Razi Vaccine and Serum Research Institute, Karaj, 2008. [In Persian].
30. Khoban H, Feyzolahi S. Prevalence of pediculosis capitis in the schools covered by health center of Shahid Bolandian of the Qazvin city in 2008. Articles abstract book of the sixth national conference and the first regional congress of Parasitology and parasitic diseases, Razi Vaccine and Serum Research Institute, Karaj, 2008. [In Persian].
31. Rafinejad J, Nourollahi A, Javadian A, Kazemnejad A, Shemshad KH. [Epidemiology of head louse infestation and related factors in school children in the county of Amlash, Guilan province, 2003-2004]. Iranian Journal of Epidemiology 2006; 2(3 and 4):51-63. [In Persian].

Original Article

Safety and efficacy of percutaneous nephrolithotomy in patients treated with chronic anticoagulant / antiplatelet therapy

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ABSTRACT

Objective: We aimed to evaluate the effects of chronic anticoagulant / antiplatelet (AC/AP) therapy on complications and surgical outcomes during and after percutaneous nephrolithotomy (PCNL) operation.
Design: Retrospective study
Setting: Tepecik Training and Research Hospital, Urology Department, Izmir, Turkey
Subjects: We reviewed the records of 268 patients that underwent PCNL operation at our institution from October 2014 to July 2017 and identified 34 patients that were being treated with chronic AC/AP therapy.
Intervention: Patients were divided into two groups: chronic AC/AP therapy and no AC/AP. The chronic AC therapy (rivaroxaban) was discontinued for three days prior to the operation. Low-molecular-weight heparin treatment was initiated during the interim period and AC therapy was resumed five days postoperatively. Meanwhile, the patients on chronic AP therapy (aspirin, clopidogrel, cilostazol) had their medication withheld for three to seven days preoperatively and the therapy was resumed five days postoperatively.
Main outcome measure: We compared the outcomes and complications in patients who were on chronic AC/AP therapy to those in control patients.
Results: A total of 34 patients (12.6%) were on chronic AC/AP therapy and 234 (87.4%) patients were not on AC/AP therapy. The comparison between AC/AP therapy and control groups did not reveal any significant differences in terms of stone-free percentage, bleeding and infection complications (P=.845, P>.05, respectively).
Conclusion: PCNL surgery can be performed safely and effectively in patients who are on chronic AC/AP therapy with careful perioperative management of anticoagulation.

KEY WORDS: anticoagulant therapy, antiplatelet therapy, percutaneous nephrolithotomy, urolithiasis

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is a standard operation in the following cases: staghorn stones larger than 20 mm, stones resistant to shock wave lithotripsy, cystine stones, patients with anatomically anomalous upper urinary system, patients with anatomical defects (scoliosis, kyphosis or spasticity), lower pole stones larger than 15 mm, and stones in transplant kidneys[1,2]. Bleeding is a major complication in PCNL operations, and transfusion rates of up to 34% during the perioperative and postoperative period have been reported[3-7]. Complications such as arteriovenous fistula and pseudoaneurysm are also the most common cause of delayed postoperative hemorrhage and may occur in approximately 1% of all PCNL cases[8,9].

In recent years, the increased life span of patients with atrial fibrillation and coagulation disorders, successful heart valve replacement therapies, and an increased number of patients with cardiac stents in the general population has led to an increase in the chronic use of anticoagulant / antiplatelet (AC/AP) therapy[10,11]. Chronic AC/AP treatment and having

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multiple comorbidities may increase the risk of surgery as well as American Society of Anesthesiology scores in these patients.

Cessation of AC/AP therapy prior to high-risk urological procedures such as PCNL, shock wave lithotripsy and percutaneous nephrostomy, as well as the surgery-related tendency for thrombosis may lead to postoperative thromboembolic complications[12]. The risk of postoperative thrombosis due to the interruption of AC/AP treatment on the one side, and increased risk of bleeding due to PCNL operation on the other side, raises a dilemma in the resumption of antithrombotic therapy in the postoperative period. In this study, we aimed to compare the complications (bleeding, infection, thromboembolism) and treatment success of patients receiving chronic AC/AP therapy with control patients who are not receiving AC/AP therapy during and after PCNL operation.

SUBJECTS AND METHODS

We retrospectively reviewed the records of 277 patients over the age of 18 years, who underwent PCNL surgery in our urology clinic between October 2014 and July 2017. Local ethics committee approved our study. Patients were divided into two groups: AC/AP therapy and not on AC/AP therapy. The AC/AP therapy distributions and the indications for chronic AC/AP therapy in these patients are shown in Table 1.

Demographic data, changes/adjustments made during the operation, and surgical outcomes were obtained from patient records. Complete blood count, serum creatinine, coagulation parameters and urine culture of each patient were evaluated before the surgery. Patients with sterile urine culture were taken into operation. All patients were assessed by direct urinary system graphy and unenhanced computerized tomography before the surgery. The stone size was calculated by multiplying the widest width and height of the stone. In patients that had multiple stones in their urinary system, the stone sizes were calculated separately and added. In our study, stones that were located in pelvis (isolated), upper calyx, middle calyx and lower calyx were classified as non-complex, while partial or whole stanghorn stones and stones located in both renal pelvis and calyx were classified as complex stones.

Patients that were receiving AC/AP therapy were divided into three groups according to venous thromboembolism risk classification model[13] (Table 2). Consults with appropriate departments were done depending on the patients' indications, and based on the type of AC/AP agent used and thromboembolism risk, the treatments were either stopped or bridging therapy was implemented. The AC therapy was discontinued for three days before the operation in one patient that was receiving AC therapy (rivaroxaban) for deep venous thrombosis. This patient was on low-molecular-weight heparin during the interim period and the AC therapy was resumed at five days postoperatively. Medications were withheld for three to seven days preoperatively in patients on AP therapy (aspirin, clopidogrel, cilostazol) and resumed at five days postoperatively. An expert anesthesiologist evaluated all patients before their surgeries. The risk of surgery was determined according to the American Society of Anesthesiology classification score.

Four different surgeons that had previously successfully performed at least 50 PCNL operations on adults performed all surgeries. All PCNL operations were performed in the prone position under general anesthesia. A single dose of appropriate intravenous antibiotic was administered before the general anesthesia in all patients. The ureteral catheter was placed via cystoscopy, fixed to the foley catheter and urinary system access was gained with fluoroscopy. Tract dilation up to 30-French was achieved with

Table 1: Distribution of patients using AC/AP therapy

AC/AP therapy etiology	No. of patients n(%)
Aspirin	25 (73.5)
Coronary Artery Disease	
Bypass	2
Stent	3
Medical Treatment	10
Hypertension	6
Cerebrovascular occlusion (SVO)	3
Chronic Kidney Disease (CDC)	1
Aspirin+Clopidrogel	6 (17.6)
Coronary Artery Disease	
Bypass	3
Stent	3
Cilostazol+Clopidrogel	2 (5.8)
Arterial Fibrillation	2
Rivaroxaban	1 (2.9)
Deep Venous Thrombus	1

AC/AP: anticoagulant / antiplatelet therapy; SVO: small-vessel occlusion; CDC: Centers for Disease Control and Prevention;
Patients that were receiving AC/AP therapy were divided into three groups according to venous thromboembolism risk classification model

Table 2: Venous thromboembolism (VTE) according to patient risk factors

Low risk	Intermediate risk	High risk
No risk factors	Any one of the following: 1. age 75 years or more; 2. Body mass index 35 or more; 3. VTE in 1st degree relative (parent, full sibling or child)	Prior VTE Patients with any combination of two or more risk factors

Amplatz dilator. Then, a 30-French plastic ampatz sheath was placed. A 26-French rigid nephroscopy was used in all cases. Stone fragmentation was done with ultrasonic lithotripter. A 24-French nephrostomy tube was used when drainage was necessary. Surgical complications in AC/AP therapy and control groups were compared with modified Clavien classification system. All patients underwent non-contrast computed tomography at their postoperative one-month visit and overall stone-free rate was evaluated.

Mean ± SD and median (minimum-maximum) were given as descriptive statistics for the numerical variables in the groups, and number (%) was given as descriptive statistics for the categorical variables. The non-parametric Mann-Whitney U test was used to determine whether there was a difference in numerical variables between the groups, while Pearson Chi-Square and Fisher Exact Test were used to compare categorical variables between groups. For all tests, the probability of Type I error was set to α=0.05. All statistical analyses were done by using the R Project 3.2.5 package program.

RESULTS

Among these 277 patients, nine patients with missing records were excluded from the study. We identified 34 patients that were receiving AC/AP therapy and 234 patients who were not on AC/AP therapy. Of the patients that were receiving AC/AP therapy, 32 patients were in the low risk, one patient was in the intermediate risk and one patient was in the high risk group according to venous thromboembolism risk classification model. The AC/AP therapy distributions and the indications for chronic AC/AP therapy in these patients are shown in Table 2. All of these patients had normal coagulation parameters prior to operation.

The mean age, gender, stone laterality, mean stone burdens, the ratio of complex to non-complex stones, mean duration of operation, changes in hemoglobin levels, the average number of access, mean hospital stay and one-month stone-free rates of both groups were compared and are shown in Table 3.

The mean age of the AC/AP therapy group was higher than that of the control group (mean age 64.6±6.6 vs 53.7±15.4 years) and this difference was statistically significant (*P*<.001). In AC/AP therapy group, the non-complex stone ratio and complex stone ratios were 29.4% and 70.6%, respectively. Meanwhile, in the control group, the non-complex stone ratio and complex stone ratios were 51.2% and 48.7%, respectively. Thus, there was a significant difference between groups in terms of stone complexity ratio (noncomplex stone/complex stone, *P*=.017). There was no significant difference between groups in terms of stone size, mean operation time, changes in hemoglobin levels, mean access numbers, and mean hospital stay (*P*=.332, *P*=.211, *P*=.340, *P*=.054 and *P*=.213, respectively). The overall stone-free rates of the groups were 70.6% for patients with AC/AP therapy and 67.9% for patients without AC/AP therapy. The comparison between the AC/AP therapy and the control groups at one-month follow-up did not reveal any significant difference in terms of stone-free percentage (*P*=.845).

There was no significant difference between groups in terms of bleeding (hematuria and blood transfusion) and infection (*P*>.05, Table 3). None of the patients developed thromboembolic complications such as

Table 3: Patients' demographic data and per operative-post operative outcomes

Variable	AC/AP	No AC/AP	*P*-value
Number of patients n(%)	34 (12.6%)	234 (87.3%)	-
Age			<.001[a]
Mean ± SD	64.56±6.593	53.72±15.362	
Median (min-max)	65.5(44-78)	56(18-93)	
Male/Female	22/12	147/87	.831[b]
Laterality (R/L)	14/20	96/138	.987[b]
Stone size (mm)			.332[a]
Mean ± SD	556.1±516.374	461.63±377.154	
Median (min-max)	417.5(126-2772)	336(60-2275)	
Stone complexity ratio	10/24	120/114	.017[b]
Operative time			.211[a]
Mean ± SD	98.97±32.608	93.23±36.489	
Median (min-max)	92.5(55-180)	85(40-230)	
Hemoglobin change			.340[a]
Mean ± SD	1.63±1.176	1.89±1.413	
Median (min-max)	1.45(-0.2-6.10)	1.6(-0.8-8.7)	
Access number			.054[a]
Mean ± SD	1.26±0.448	1.16±0.440	
Median (min-max)	1(1-2)	1(1-4)	
Length of stay (days)			.213[a]
Mean ± SD	2.73±1.442	3.05±1.707	
Median (min-max)	2(2-8)	2(2-10)	
Clinic stone free rates n(%)	24/34 (70.6%)	159/234 (67.9%)	.845[b]
Bleeding complications			
Hematuria	1/34	1/234	-
Blood transfusion	2/34 (5.8%)	20/234 (8.5%)	>.05[c]
Urinary tract infection	2/34 (5.8%)	15/234 (6.4%)	>.05[c]
Arteriovenous fistula	1	1	-

[a]Mann-Whitney U Test; [b]Perason Chi-Square Test; [c]Fisher's Exact Test; AC/AP: anticoagulant / antiplatelet therapy

Table 4: The distribution of ASA risk scores

ASA risk score	Patients on AC/AP n(%)	Patients not on AC/AP n(%)	*P*-value
ASA 1	0 (0%)	97 (41.5%)	<.001[a]
ASA 2	20 (58.8%)	120 (51.3%)	
ASA 3	14 (41.2%)	17 (7.3%)	

[a]Pearson Chi-Square Test; AC/AP: anticoagulant / antiplatelet therapy; ASA: American Society of Anesthesiology

myocardial infarctions, stroke, transient ischemic attack, peripheral arterial thrombosis or mortality through the last follow-up. There was a significant difference between groups in terms of distribution of American Society of Anesthesiology 1, 2 and 3 risk scores (P<.001, Table 4).

DISCUSSION

In patients using chronic AC/AP therapy, perioperative regulation of medications is defined by four options in the European Urological Guidelines[13]. In procedures with high bleeding risk such as PCNL, extracorporeal shock wave lithotripsy and percutaneous nephrostomy, one of the options mentioned above is applied after assessing the patient's venous thromboembolism risk (low, moderate, high). In our study, in patients that underwent PCNL surgery, chronic AC/AP medications were either interrupted or bridged, in accordance with guidelines.

Bleeding is one of the major complications of both intraoperative and postoperative procedures for any patient who has undergone PCNL surgery and does not receive AC/AP therapy. In the literature, 7% (0-20) of patients had bleeding that required transfusion[14]. Blood transfusion rates vary in the literature in patients with renal stones that underwent PCNL surgery and were receiving AC/AP treatment that was discontinued prior to PCNL surgery. Kefer *et al* reported seeing postoperative bleeding complications in 7% (2/27) of patients receiving AC/AP therapy, whereas in the study by Nerli *et al*, this rate was 19.4% (7/36)[12,15]. In our study, this ratio was determined as 5.8% in AC/AP therapy group and 8.5% in the control group.

Cessation of chronic AC/AP therapy prior to PCNL surgery may cause predisposition to a number of thromboembolic complications[12]. Recent studies have reported using low-dose aspirin therapy during PCNL operations because of the risks of thromboemboli. Otto *et al* have compared surgical outcomes of 67 patients who underwent PCNL surgery and were administered low-dose aspirin perioperatively with 207 patients who did not use aspirin. There was no significant difference in terms of bleeding complications, transfusions rates and stone-free rates between the low-dose aspirin and control groups[16]. In a study conducted by Leavitt *et al*, 16 high cardiac risk patients with chronic aspirin therapy underwent PCNL without cessation of aspirin treatment. While bleeding requiring transfusion was seen in three patients (18.8%), no thromboembolic complications were detected in any of the patients[17]. In a prospective study where 30% of all participants were urologic patients, the perioperative use of aspirin produced 7.2% (9% vs 1.8%) reduction in the absolute risk of major postoperative cardiac side effects. Moreover, no difference was detected in terms of estimated blood loss, the surgeon's perception of bleeding tendency, blood product transfusion requirements or severe bleeding complications[18]. Although perioperative aspirin treatment is reported to be effective and safe in PCNL surgery, the recommendation of the European Urology Guideline is that chronic aspirin therapy should be stopped prior to surgery. Larger, prospective studies are needed to investigate the effects of perioperative chronic aspirin therapy in patients undergoing PCNL surgeries.

PCNL surgery is contraindicated for patients with bleeding diathesis due to high risk of bleeding. As stated in the European Urological Guideline, "In the case of an uncorrected bleeding disorder or continued AC/AP therapy, ureterorenoscopy (URS) is an alternative option''[13]. In the study conducted by Turna *et al*, the data of 37 patients who underwent flexible URS operation and were using chronic AC/AP medications were compared with the control group that was not receiving AC/AP therapy. There was no significant difference in terms of per operative-post operative complication rates and stone-free rates between the two groups. Holmium YAG laser lithotripsy and flexible URS are known to be effective and safe in patients with renal stones and chronic AC/AP therapy[19]. In a meta-analysis by Sharaf *et al*, they reported that URS operations with or without laser is a safe and effective treatment option, even in urolithiasis patients with hemorrhagic diathesis disorder or chronic AC/AP therapy[20]. While PCNL and flexible URS treatment options are available for some kidney stone patients, flexible URS surgery may not be appropriate for patients with staghorn stones, infection-related stones, narrow angle lower calyx stones, and patients with urinary diversion or transplanted kidney. Since PCNL surgery is more appropriate for these patients in particular, chronic AC/AP treatment of patients should be performed in conjunction with the guidelines[17-22].

Complex stones are more common in elderly and high-risk patients. The reason for this is that both the surgeon and these patients prefer conservative treatment to surgery and thus, the stone fragments may reach larger size and become staghorn formation[23]. In our study, the age, complexity ratio and stone size of the patients in the AC/AP therapy group were higher compared to the control group. Although patients receiving chronic AC/AP therapy were older and had a higher number of comorbidities, the complication rates during and after PCNL surgery were statistically similar between the two groups.

Long-term AP treatment is often used to prevent thromboembolic complications such as deep venous thrombosis, atrial fibrillation, heart valve disease and coronary artery disease[24]. Comparison of atrial fibrillation patients with and without chronic AP

use showed that in patients that received coumadin and aspirin treatment, the relative stroke risk ratios decreased by 68% and 21%, respectively[25]. It has also been shown that aspirin therapy reduces the risk of mortality after myocardial infarction and reduces mortality in patients with high risk for cardiovascular disease, angina, stroke or transient ischemic attack[26]. Similarly, clopidogrel, an oral AP agent, is widely used as an adjunctive therapy to prevent subacute thrombosis after coronary stenting[27].

The first limitation of this study is that it was a single center study performed retrospectively. Our second limitation is that although the diameter of the access sheath is gradually reduced in PCNL surgeries, we have used 30F sheath in our study.

CONCLUSION

We believe that with careful perioperative management of anticoagulation, PCNL surgery can be performed safely and effectively in patients who are on chronic AC/AP therapy. Thus, in accordance with the current guidelines and with multidisciplinary approach of relevant branches, urologists and anesthesiologists, the cessation and subsequent re-initiation of chronic AC/AP treatment may safely be applied in PCNL operations with minimal concern for bleeding and thromboembolic complications.

REFERENCES

1. Morris DS, Taub DA, Wei JT, Dunn RL, Wolf JS Jr, Hollenbeck BK. Regionalization of percutaneous nephrolithotomy: Evidence for the increasing burden of care on tertiary centers. J Urol 2006; 176(1):242-246.
2. Srirangam SJ, Darling R, Stopford M, Neilson D. Contemporary practice of percutaneous nephrolithotomy: A review of practice in a single region of the UK. Ann R Coll Surg Engl 2008; 90(1):40-44.
3. Roth RA, Beckmann CF. Complications of extracorporeal shock-wave lithotripsy and percuteanous nephrolithotomy. Urol Clin North Am 1988; 15(2):155-166.
4. Lang EK. Percutaneous nephrostolithotomy and lithotripsy: A multi-institutional survey of complications. Radiology 1987; 162(1 Pt 1):25-30.
5. Clayman RV, Surya V, Hunter D, Castaneda-Zuniga WR, Miller RP, Coleman C, *et al*. Renal vascular complications associated with the percutaneous removal of renal calculi. J Urol 1984; 132(2):228-230.
6. Stoller ML, Wolf JS Jr, St Lezin MA. Estimated blood loss and transfusion rates associated with percutaneous nephrolithotomy. J Urol 1994; 152(6 Pt 1):1977-1981.
7. Aron M, Yadav R, Goel R, Kolla SB, Gautam G, Hemal AK, *et al*. Multi-tract percutaneous nephrolithotomy for large complete staghorn calculi. Urol Int 2005; 75(4):327-332.
8. Davidoff R, Bellman GC. Influence of technique of percutaneous tract creation on incidence of renal hemorrhage. J Urol 1997; 157(4):1229-1231.
9. Patterson DE, Segura JW, LeRoy AJ, Benson RC Jr, May G. The etiology and treatment of delayed bleeding following percutaneous lithotripsy. J Urol 1985; 133(3):447-451.
10. Rowen SB, Bailey DN, Bublitz CE, Anderson RJ. Trends in anticoagulation for atrial fibrillation in the U.S.: An analysis of the National Ambulatory Medical Care Survey Database. J Am Coll Cardiol 2007; 49(14):1561-1565.
11. Starr A, Fessler CL, Grunkemeier G, He GW. Heart valve replacement surgery: Past, present and future. Clin Exp Pharmacol Physiol 2002; 29(8):735-738.
12. Kefer JC, Turna B, Stein RJ, Desai MM. Safety and efficacy of percutaneous nephrostolithotomy in patients on anticoagulant therapy. J Urol 2009; 181(1):144-148.
13. Tikkinen KAO, Cartwright R, Gould MK, Naspro R, Novara G, Sandset PM, *et al*. EAU guidelines on thromboprophylaxis in urological surgery; 2017. Available from: http://www.uroweb.org/guidelines/.
14. Seitz C, Desai M, Häcker A, Hakenberg OW, Liatsikos E, Nagele U, *et al*. Incidence, prevention, and management of complications following percutaneous nephrolitholapaxy. Eur Urol 2012; 61(1):146-158.
15. Nerli RB, Reddy MN, Devaraju S, Hiremath MB. Percutaneous nephrolithotomy in patients on chronic anticoagulant/antiplatelet therapy. Chonnam Med J 2012; 48(2):103-107.
16. Otto BJ, Terry RS, Lutfi FG, Syed JS, Hamann HC, Gupta M, *et al*. The effect of continued low dose aspirin therapy in patients undergoing percutaneous nephrolithotomy. J Urol 2018; 199(3):748-753.
17. Leavitt DA, Theckumparampil N, Moreira DM, Elsamra SE, Waingankar N, Hoenig DM, *et al*. Continuing aspirin therapy during percutaneous nephrolithotomy: unsafe or under-utilized? J Endourol 2014; 28(12):1399-1403.
18. Oscarsson A, Gupta A, Fredrikson M, Jarhult J, Nystrom M, Pettersson E, *et al*. To continue or discontinue aspirin in the perioperative period: A randomized, controlled clinical trial. Br J Anaesth 2010; 104(3):305-312.
19. Turna B, Stein RJ, Smaldone MC, Santos BR, Kefer JC, Jackman SV, *et al*. Safety and efficacy of flexible ureterorenoscopy and Holmium:YAG lithotripsy for intrarenal stones in anticoagulated cases. J Urol 2008; 179(4):1415-1419.
20. Sharaf A, Amer T, Somani BK, Aboumarzouk OM. Ureteroscopy in patients with bleeding diatheses, anti-coagulated and on anti-platelet agents: A systematic review and meta-analysis of the literature. J Endourol 2017; 31(12):1217-1225.
21. Riley JM, Averch TD. Stone management for the patient on anticoagulation. Curr Urol Rep 2012; 13(3):187-189.
22. Sari S, Ozok HU, Topaloglu H, Cakici MC, Ozdemir H, Karakoyunlu AN, *et al*. The association of a number of anatomical factors with the success of retrograde intrarenal surgery in lower calyceal stones. Urol J 2017; 14(4):4008-4014.

23. Nouralizadeh A, Lashay A, Ziaee SA, Ahanian A, Sharifi SHH, Nikkar MM, *et al*. Percutaneous nephrolithotomy in high-risk patients: A single-center experience with more than 350 cases. Urol Int 2013; 90(4):394-398.
24. du Breuil AL, Umland EM. Outpatient management of anticoagulation therapy. Am Fam Physician 2007; 75(7):1031-1042.
25. Fang MC, Singer DE. Anticoagulation for atrial fibrillation. Cardiol Clin 2004; 22:47-62.
26. McAlister FA, Lawson FM, Teo KK, Armstrong PW. Randomised trials of secondary prevention programmes in coronary heart disease: systematic review. BMJ 2001; 323(7319):957-962.
27. Doggrell SA. Clopidogrel use with stenting. Expert Opin Pharmacother 2007; 8(9):1399-1402.

Original Article

Simultaneous resection of a bladder tumor and prostate is oncologically and functionally safe

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ABSTRACT

Objective: The aim of this study is to compare the outcomes of patients who underwent simultaneous transurethral resection of the prostate (TURP) and transurethral resection of bladder tumor (TURBT) with those who underwent only TURBT.
Design: Historical-cohort
Setting: Department of Urology, Ege University School of Medicine, Turkey
Subjects: One hundred and eighty-six patients who underwent TUR were included in the study.
Intervention: Tumor characteristics, complication, recurrence and progression rates, recurrence localizations, and elapsed time to recurrence were compared between the groups.
Main outcome measures: Outcomes of simultaneous resection
Results: The bladder tumor recurrence rate was 36.6% for group A and 29.8% for group B (*P*=.068), and the progression rates were 8.2% and 6.4%, respectively (*P*=.084). There was no significant difference between the elapsed time to recurrence (8.28±1.17 vs. 6.54±1.28 months) and the rate of prostatic urethral recurrence (1.8% vs. 1.7%, *P*=.712 and *P*=.395, respectively). Complication rates and progression distribution of tumors were also similar in both groups.
Conclusion: It is safe to resect an incidentally detected bladder tumor along with prostate resection, with similar rates of progression, recurrence, and complications.

KEY WORDS: benign prostatic hyperplasia, bladder tumor, progression, recurrence, transurethral resection

INTRODUCTION

Bladder cancer is the fourth most common cancer and the eighth most common cause of cancer death among men[1]. About 50 - 70% of bladder tumors (BT) treated with transurethral resection will recur, while 15% will progress[2]. Benign prostatic hyperplasia (BPH), although not a fatal disease, causes distressed lower urinary tract symptoms, and it is highly prevalent among men >50 years of age[3]. Transurethral resection of the prostate (TURP) is still the gold standard for the surgical treatment of symptomatic BPH[4]. Likewise, currently, the first-line therapy for bladder tumors is transurethral resection (TURBT).

The concomitant BT with bladder outlet obstruction induced by BPH leads to an adverse prognosis. The clinical scenario of a male patient undergoing TURP who also requires TURBT is not usual. Most urologists prefer to perform TURBT and TURP in different sessions due to concern of implanting tumor cells in resected prostate tissue[5]. On the other hand, there are many urologists who believe that the two procedures do not have any negative effect when combined in the same session[6-8]. Those who advocate that it is safe to perform the two procedures in the same session believe that by eliminating bladder outlet obstruction, the residual urine volume is reduced, so that the exposure of the bladder by circulating tumor cells is reduced[9]. However, those with the opposite view suggest that circulating tumor cells may implant on the resected prostate surface, and recurrence rate of bladder tumor may increase as a result of treating both diseases in the same session[5].

In this study, to contribute to this ongoing debate, we compared the outcomes of patients who

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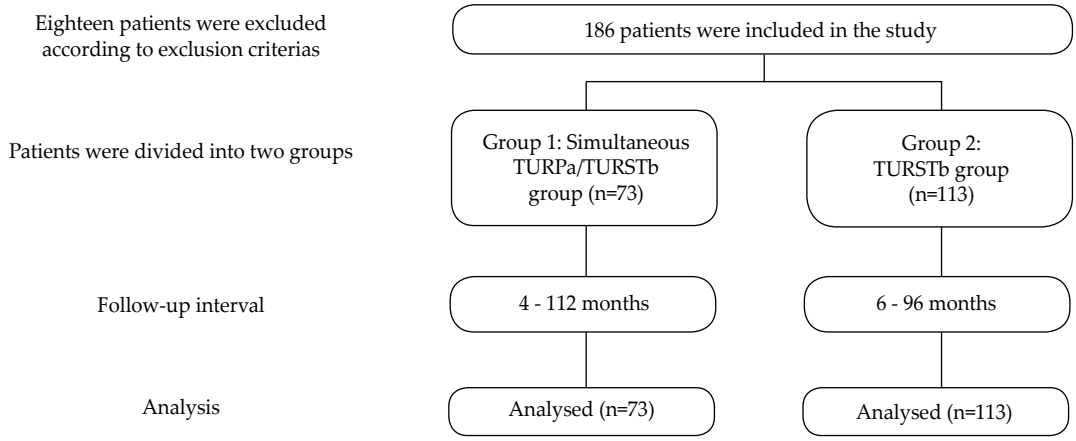

[a]transurethral resection of the prostate
[b]transurethral resection of bladder tumor

Fig 1: Study flow chart

were treated with simultaneous endoscopic TURP and TURBT due to symptomatic, clinical BPH and incidentally detected bladder tumors with the outcomes of patients treated with TURBT alone in the same time period. The two groups were compared in many aspects, including oncological outcomes. To our knowledge, this is the first study evaluating the safety of resection of incidentally detected bladder tumors encountered during TURP.

SUBJECTS AND METHODS

Study population

One hundred and eighty-six patients were included in this study (Figure 1). Seventy-three patients underwent simultaneous TURP and TURBT (Group A) and 113 patients underwent TURBT (Group B). The patients were operated between January 2006 and December 2016. The mean follow-up period of the patients was 73.8 months (range: 4.2-118.6 months). Patients' data were obtained from patient files. The patients had no previous history of urological surgery. The decision of surgical treatment for BPH was made according to the absolute and relative indications suggested by the European Association of Urology guidelines[10] (Table 1). Detection of a bladder mass in imaging methods (ultrasound or computed tomography) and/or diagnostic cystoscopy with painless, macroscopic hematuria symptoms were the indications for TURBT. Being older than 18 years and having an indication for TURP/BT were the inclusion criteria. Previous urological surgery and urological malignancy history, being reluctant for the operation, and refusing to sign the informed consent form prior to operation were the exclusion criteria (n=18). Written consent was obtained prior to the operation, including that patients' medical records could be used in clinical trials, provided that their identity was kept confidential and the study was conducted in compliance with the principles of the Declaration of Helsinki.

This study was a historical cohort trial which was performed in a third step referral university hospital's urology clinic.

Surgical technique

Negative urine culture was provided prior to surgery. Conventional monopolar TUR was performed with a 24 Fr Karl Storz® (Tuttlingen, Germany) non-continuous flow resectoscope using

Table 1: Indications for surgical treatment recommended by European Association of Urology guidelines for benign prostatic hyperplasia

Absolute operation indications	Relative operation indications
Recurrent or refractory urinary retention Overflow incontinence Recurrent UTIs[a] Bladder stones or diverticula Treatment-resistant macroscopic haematuria due to BPH/BPE[b] Dilatation of the upper urinary tract due to BPO[c], with or without renal insufficiency	Absence of adequate relief from LUTS[d] or PVR[e] using conservative or medical treatments

[a]Urinary tract infections; [b]Benign prostatic hyperplasia / Benign prostatic enlargement; [c]Benign prostatic obstruction; [d]Lower urinary tract symptoms; [e]post void residual urine volume

5% mannitol irrigation solution. All instruments were calibrated. Electroresection and coagulation for TURP and TURBT is performed by a monopolar, high-frequency current with a maximum cutting power of 200 W and 120 W, and coagulation power of 120 W and 80 W, respectively. Different urologists with similar experience performed the operations. A single dose of 1 gr cefazolin was administered with the induction of anesthesia as prophylactic intravenous antibiotic treatment. Most of the patients were operated under spinal anesthesia. Twenty mg furosemid was administered to patients intravenously to prevent the TUR syndrome. A 22 Fr 3-way Foley catheter was introduced to the bladder at the end of the procedure. The catheter balloon was inflated to 45 ml with saline and retracted backward, thus allowing traction to the bladder neck for hemostasis. After two hours, the traction was loosened and the catheter was allowed to reach it's normal position. Saline irrigation was continued until obtaining a clear urine color and the catheter was removed after three to five days in the presence of clear urine without irrigation. Patients were monitored for a while until they were able to void normally and then discharged. Follow-up visits were performed every three months in the first year, and every six months thereafter.

Outcome assessment

Primary outcome measurements were comparison of recurrence and progression rates between the two groups. Secondary outcome measurements were comparison of complication rates, locations of recurrences in the bladder and elapsed time to recurrence. Complications were assessed according to the Clavien-Dindo classification system. Number of tumors, size and prior recurrence rate were assessed for recurrence rate, and T category, grade and presence of CIS were assessed for progression rate. Bladder mapping was performed using endoscopy for recurrence localization. "Elapsed time to recurrence" was determined by calculating the time from resection date to recurrence.

Statistical analysis

We used Yamane's formula[11] to calculate our sample size. This formula uses a 95% confidence level and *P*=.05 are assumed. Data were analyzed using the SPSS (version 23.0) statistical program. Variables were compared using chi-square and Student's t test. Relative risk and 95% confidence interval were calculated for recurrence and progression data. A value of *P*<.05 was considered statistically significant.

RESULTS

A total of 186 patients' data were evaluated. The mean age of the second group was slightly lower than the first group (*P*=.042). In the first group, T2 pathology was not detected in any of the patients, whereas it was detected in nine patients (7.9%) in the second group (*P*=.021). These patients were excluded from the follow-up protocol used in the study. Radical cystectomy and urinary diversion was performed in seven patients and radiotherapy in two patients. In the first group, the number of BT was not more than three in any patient. In the second group, three to five tumors were detected in four patients (3.5%), but this was not significant (*P*=.065). Complication rates were similar, no complications were seen in any of the patients with Grade IV and above (Table 2).

There was no significant difference between the groups in terms of recurrence and progression rate, prostatic urethral recurrence rate, and time elapsed to recurrence (Table 3). Progression was seen in six

Table 2: Demographic data and prostate and bladder tumor characteristics

Characteristics[a]	Group A	Group B	*P*[f]
Number of patients	73	113	
Age (years)	62.07±8.1	48.12±7.4	.042
BMI[b] (kg/m^2)	27.8±0.7	24.4±0.8	.742
Male gender	73 (100)	88 (77.8)	.541
Smoking			.119
Yes	48 (65.7)	66 (58.4)	
Amount (cigarettes/day)			
1-10	14 (29.1)	18 (27.2)	
10-20	24 (50.0)	29 (43.9)	
>20	10 (20.9)	19 (28.9)	
Tumor diameter (cm)	1.9±0.6	2.3±0.8	.214
T stage			.465
Ta	49 (67.1)	68 (60.2)	
T1	24 (32.9)	36 (31.9)	
T2	0	9 (7.9)	.021
Grade			.344
Low	51 (69.9)	70 (61.2)	
High	22 (30.1)	43 (38.8)	
Tumor number			.254
Solitary	62 (84.9)	89 (78.8)	
1-3	11 (15.1)	20 (17.7)	
3-5	0	4 (3.5)	
PSA[c] (ng/mL)	1.98±0.86		
Q max[d] (mL/s)	6.4±2.2		
PVR[e] (mL)	66±12.8		
Complication rate[g]			.482
Grade I	9 (12.4)	13 (11.8)	
Grade II	6 (8.2)	8 (7.5)	
Grade IIIA	2 (2.6)	2 (1.9)	
Grade IIIB	1 (1.8)	2 (1.5)	

[a]Data is given as mean ± SD or number (percent); [b]Body mass index; [c]Prostate-specific antigen; [d]Maximum flow rate measured in uroflowmetry; [e]Post void residual urine volume; [f]Significant values are written in italics; [g]Complications were grouped according to the Clavien Dindo classification system

Table 3: Comparison of groups in terms of tumor recurrence and progression

Variables[a]	Group A	Group B	RR[b]	95% CI[c]	*P*
Number of patients	73	113			
Recurrence rate	26 (36.6)	33 (29.8)	1.28	0.34 - 6.54	.068
Time elapsed to recurrence (months)	8.28±1.17	6.54±1.28			.712
Progression rate	6 (8.2)	7 (6.4)	1.33	0.26 - 7.38	.084
Recurrence in prostatic urethra	1 (1.8)	2 (1.7)	1.12	0.42 - 6.42	.395

[a]Data is given as mean ± SD or number (percent); [b]Relative risk; [c]Confidence interval

patients in group A and in seven patients in group B. In group A, three patients progressed from TaLG (low grade) to TaHG (high grade), two patients from TaLG to T1HG, and one patient from T1LG to T1HG, respectively. In group B, one patient progressed from TaLG to TaHG, four patients progressed from TaLG to T1HG, and two patients showed progression from T1LG to T1HG (Table 4).

Table 4: Comparison of groups in terms of progression distribution

Stage and grade progression[a]	Group A	Group B	*P*
Recurrent tumors with progression	6/73	7/113	.426
TaLG[b] to TaHG[c]	3/6	1/7	
TaLG[b] to T1HG[c]	2/6	4/7	
T1LG[b] to T1HG[c]	1/6	2/7	

[a]Values are given as numbers; [b]Low-grade; [c]High-grade

DISCUSSION

Although superficial bladder tumors are not life-threatening (as long as they remain superficial), recurrence and progression of these tumors are frequent problems. There are some prognostic factors predicting these risks[12]. Patients are assigned to risk groups using the risk tables recommended by the European Association of Urology guidelines, and follow-up frequency and method are determined according to these risk groups[13,14]. However, despite all follow-up regimens, a significant proportion of the patients will recur and show progression[15].

In patients with lower urinary tract symptoms, upper urinary tract ultrasonography is not recommended by the European Association of Urology guidelines unless there is a high amount of residual urine, hematuria, or urolithiasis history[16,17]. Also, the guidelines recommend urethrocystoscopy when there is a suspicious bladder or urethral pathology, prior to surgical treatment, and if the findings will change the treatment. However, since urethrocystoscopy is an invasive diagnostic method, most urologists do this in the same session with prostate surgery and decide on the treatment method (endoscopic/open). We often manage our patients in this way in our clinical practice. Preoperative ultrasound imagings from different centers may also have broad variations and often cannot accurately demonstrate prostate volume and additional pathologies. For this reason, to make decisions about the surgical method based on only preoperative ultrasonographic findings may mislead the urologists.

In fact, simultaneous resection of the prostate and bladder tumor is not a newly evaluated issue in the literature. There are a large number of studies and reviews comparing simultaneous TURBT and TURP with TURBT alone, as we discussed below. This is probably the first study analyzing the outcomes of concurrent resection of a bladder tumor that was detected simultaneously in patients who were primarily planned for prostate resection. Detection of a bladder tumor during prostate surgery is uncommon because, the diagnosis of bladder tumor can be made preoperatively by ultrasonography, a simple and non-invasive imaging method. There were some reasons why we diagnosed bladder cancer incidentally in our patients. First, as mentioned above, ultrasound is not absolutely recommended before prostate surgery unless patients have some special circumstances (high amount of residual urine, hematuria, *etc*.). Secondly, indications that require prostate surgery in our patients were not hematuria, which is a finding that strongly suggests bladder tumor and requires further investigation. Third, due to the high patient volume at the radiology department of our hospital, the ultrasound appointments are given too late and patients may be forced to have the ultrasounds that we want to evaluate prostate volume in a suboptimal manner in different centers. Eventually, in the last 10 years, we have identified simultaneous bladder tumor in 73 patients who underwent operation with primary intent of TURP and the bladder tumor was simultaneously resected in these patients.

Studies evaluating the safety of performing TURBT and TURP together reported different results. The fulcrum of studies reporting negative results is that irrigation fluid is spread by blood or lymphatic circulation due to high intravesical pressure during TUR and tumor cells are implanted in traumatized areas[6,18]. Boreham *et al* showed that 37.5% of patients

with bladder cancer had recurrence at prostatic urethra after TURP [19]. Similarly, Golomb *et al* showed that 39.1% of patients who underwent simultaneous TURBT and suprapubic prostatectomy had recurrences in prostate-related areas such as the prostatic urethra, bladder neck and cystostomy line[20].

On the other hand, there are a lot of publications supporting the simultaneous performance of both procedures in the literature. Tsivian *et al*[21] evaluated the effect of simultaenous TURBT and TURP on recurrences at the bladder neck and prostatic urethra. They retrospectively analyzed the records of 51 patients who underwent simultaneous resection during the 10-year study period. They divided the patients into two groups as single (n=28) and multiple bladder tumor (n=23) groups and they found that simultaneous resection did not negatively affect recurrence in the bladder neck and prostatic urethra, similar to the present study. Ugurlu *et al* performed simultaneous resection only in patients with solitary, <3 cm bladder tumor and compared the oncologic outcomes with the TURBT alone group. They found no statistically significant differences between groups in terms of recurrence, progression, recurrence in the prostatic urethra and elapsed time to recurrence[22]. Singh *et al* performed simultaneous TURBT and TURP in patients with urodynamically proven bladder outlet obstruction and compared the outcomes with patients who underwent bladder tumor and prostate resection with a six-month interval in their prospective, randomized trial, and they concluded that simultaneous resection does not increase the risk of recurrence and progression in an appropriately selected patient group[23]. The difference that distinguished this study from the others was that the resection of the two organs was performed in both groups, but at different times. Picozzi *et al* conducted a meta-analysis and included 1,234 participants in the eight studies. They concluded that both operations can be performed in the same session without exposing the patients to negative oncological outcomes. They also emphasized that patients are spared from a secondary anesthesia and prostate surgery[24]. In another meta-analysis, Luo *et al* evaluated 483 patients operated with simultaneous resection and 500 with TURBT alone. They suggested that simultaneous resection did not increase the recurrence rate in bladder neck and prostatic fossa[25]. Li *et al* assessed eight studies including a total of 1,372 patients in their systematic review and meta-analysis. They found that overall recurrence rates were lower in the TURBT+TURP group and the difference was statistically significant. The postoperative recurrence rate in the prostatic fossa, bladder neck and bladder tumor progression rates were similar between the simultaneous and only TURBT groups. Kouriefs *et al* suggested that the tumor grade and number did not significantly affect the recurrence rate in simultaneous resection patients compared to TURBT alone patients[26]. Ham *et al* evaluated the long-term outcome of simultaneous TURBT and TURP. They found that combining the two procedures in the same session may decrease cancer recurrence and delay time to recurrence without the risk of cancer implantation, especially in patients with a papillary, solitary bladder tumor less than 3 cm[27].

The utmost concern of physicians dealing with uro-oncology is the oncological safety. To achieve this, clinicians can make concessions peroperatively including major complications. Clinicians have resorted to this pathway with the intent not to sacrifice oncologic safety during simultaneous resection and to spare the patient from bladder tumor and benign prostate hyperplasia. The patient also does not have to undergo anesthesia again, and avoiding the economic burden and time loss of a secondary procedure are additional benefits of combining the two operations in one session. For this reason, surgeons have frequently preferred simultaneous resection, and this issue has been discussed extensively in the literature. The fact that it is not in a prospective, controlled manner is the main limitation of our study. Other shortcomings may be that operations are not performed by the same surgeon and other factors that may affect tumor recurrence and progression (job, habits, *etc*.) are not evaluated. On the other hand, our study is the first evaluating the safety of resection of incidentally detected bladder tumors during TURP. Relying on the results of previous studies, we did not hesitate to resect the incidental bladder tumors in these patients. We made simultaneous resection for the many reasons mentioned above; the aggressive course of transitional cell carcinoma and the feeling of being late in the tumor treatment were the most important factors determining our decision.

CONCLUSION

We concluded that bladder tumor encountered during endoscopic BPH surgery can be resected with similar recurrence, progression and complication rates when compared to tumor resection alone. Thus, patients can be avoided from the morbidities caused by re-operation and anesthesia.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68(1):7-30.
2. Lutzeyer W, Rübben H, Dahm H. Prognostic parameters in superficial bladder cancer: An analysis of 315 cases. J Urol 1982; 127(2):250-252.
3. Bushman W. Etiology, epidemiology, and natural history of benign prostatic hyperplasia. Urol Clin North Am 2009; 36(4):403-415, v.
4. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, *et al*. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol 2013; 64(1):118-140.
5. Hinman Jr F. Recurrence of bladder tumors by surgical implantation. J Urol 1956; 75(4):695-696.
6. Weyrauch HM, Crossfield JH. Dissemination of bladder neoplasms by endoscopic electroresection. Trans Am Assoc Genitourin Surg 1961; 53:6-12.
7. Kiefer JH. Bladder tumor recurrence in the urethra: a warning. J Urol 1953; 69(5):652-656.
8. Page BH, Levison VB, Curwen MP. The site of recurrence of non-infiltrating bladder tumours. Br J Urol 1978; 50(4):237-242.
9. Kang D, Chokkalingam A, Gridley G, Nyren O, Johansson JE, Adami HO, *et al*. Benign prostatic hyperplasia and subsequent risk of bladder cancer. Br J Cancer 2007; 96(9):1475-1479.
10. Gravas S, Bach T, Bachmann A, Drake M, Gacci M, Gratzke C, *et al*. EAU Guidelines on management of non-neurogenic male lower unrinary tract symptoms (LUTS), incl. Benign Prostatic Obstruction (BTO). Produced by EAU. 2015.
11. Yamane T. Elementary sampling theory. 1st ed. Englewood Cliffs, New Jersey: Prentice Hall; 1967.
12. Nargund VH, Tanabalan C, Kabir MN. Management of non–muscle-invasive (superficial) bladder cancer. Semin Oncol 2012: 39(5):559-572.
13. Fernandez-Gomez J, Madero R, Solsona E, Unda M, Martinez-Piñeiro L, Gonzalez M, *et al*. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol 2009; 182(5):2195-2203.
14. Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, *et al*. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006; 49(3):466-477.
15. Bostwick DG. Natural history of early bladder cancer. J Cell Biochem Suppl 1992; 16I:31-38.
16. Thorpe A, Neal D. Benign prostatic hyperplasia. Lancet 2003; 361(9366):1359-1367.
17. Wilkinson AG, Wild SR. Is pre-operative imaging of the urinary tract worthwhile in the assessment of prostatism? Br J Urol 1992; 70(1):53-57.
18. El-Abbady AA, Shoukry MS, Hanno AG, Younis LK, Abdel-Rahman M. Repeated transurethral resection of recurrent superficial bladder tumors: Does it affect the spread and stage of the tumor? Scand J Urol Nephrol 2002; 36(1):60-64.
19. Boreham P. The surgical spread of cancer in urology. Br J Urol 1956; 28(2):163-175.
20. Golomb J, Gorelik U, Keler T, Lindner A. Incidence and pattern of bladder tumor recurrence following combined suprapubic prostatectomy and excision of a bladder tumor. Eur Urol 1989; 16(2):86-88.
21. Tsivian A, Shtricker A, Sidi AA. Simultaneous transurethral resection of bladder tumor and benign prostatic hyperplasia: hazardous or a safe timesaver? J Urol 2003; 170(6 Pt 1):2241-2243.
22. Ugurlu O, Gonulalan U, Adsan O, Kosan M, Oztekin V, Cetinkaya M. Effects of simultaneous transurethral resection of prostate and solitary bladder tumors smaller than 3 cm on oncologic results. Urology 2007; 70(1):55-59.
23. Singh V, Sinha RJ, Sankhwar SN. Outcome of simultaneous transurethral resection of bladder tumor and transurethral resection of the prostate in comparison with the procedures in two separate sittings in patients with bladder tumor and urodynamically proven bladder outflow obstruction. J Endourol 2009; 23(12):2007-2011.
24. Picozzi SC, Ricci C, Gaeta M, Casellato S, Bozzini G, Ratti D, *et al*. Is it oncologically safe performing simultaneous transurethral resection of the bladder and prostate? A meta-analysis on 1,234 patients. Int Urol Nephrol 2012; 44(5):1325-1333.
25. Luo S, Lin Y, Zhang W. Does simultaneous transurethral resection of bladder tumor and prostate affect the recurrence of bladder tumor? A meta-analysis. J Endourol 2011; 25(2):291-296.
26. Kouriefs C, Loizides S, Mufti G. Simultaneous transurethral resection of bladder tumour and prostate: Is it safe? Urol Int 2008; 81(2):125-128.
27. Ham WS, Kim WT, Jeon HJ, Lee DH, Choi YD. Long-term outcome of simultaneous transurethral resection of bladder tumor and prostate in patients with nonmuscle invasive bladder tumor and bladder outlet obstruction. J Urol 2009; 181(4):1594-1599; discussion 1599.

Original Article

Utility of biomarkers for differentiating between diabetic retinopathy and diabetic with no retinopathy

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ABSTRACT

Objectives: No study has determined the validity of vascular endothelial growth factor A (VEGF-A) and urinary albumin to creatinine ratio (ACR) for screening for diabetic retinopathy (DR) by comparing them to optical coherence tomography (OCT). This study investigated the usefulness of these biomarkers in diagnosing DR.
Design: Cross-sectional study
Setting: Layla Qasim Diabetic Center, Erbil, Iraq
Subjects: The study included 164 patients with diabetes mellitus: 30 patients with no retinopathy as a control group, 86 patients with non-proliferative diabetic retinopathy (NPDR), and 48 patients with proliferative diabetic retinopathy (PDR), referred to the diabetic center between November 2016 and October 2017, and an ophthalmologist diagnosed them with DR using OCT. Blood and urine samples were collected from each patient.
Intervention: None
Main outcome measures: The urinary ACR and serum VEGF were measured for all patients.
Results: We measured the cut-off values of VEGF-A and ACR for screening for DR and PDR and their validity parameters. These markers differed significantly from OCT, which is considered a gold standard in diagnosing DR (*P*<.001). However, when the two markers were combined, the sensitivity and specificity were 91% and 70% respectively, and their results did not differ significantly from OCT (*P*=.664) in differentiating DR from diabetic patients with no retinopathy. Nevertheless, this combination failed to differentiate PDR from NPDR. In this case, the sensitivity increased to 95.8% whereas specificity decreased to 31.4%, and the results were significantly different from OCT results (*P*<.001).
Conclusion: Compared to OCT, the combination of serum VEGF-A and ACR exhibits reasonable diagnostic power in differentiating DR from diabetic patients with no retinopathy, although it demonstrates no significant validity for differentiating DR progression.

KEY WORDS: diabetic retinopathy, optical coherence tomography, urinary albumin to creatinine ratio

INTRODUCTION

A common microvascular complication of chronic hyperglycaemia is diabetic retinopathy (DR), which is considered the main cause of blindness[1]. In diabetes mellitus, the microvascular lesion appears in the form of capillary non-perfusion and ischemia, and upregulates angiogenic factors including vascular endothelial growth factor (VEGF-A). This stimulates pathologic neovascularization and promotes vascular permeability, subsequently causing the development of proliferative diabetic retinopathy (PDR) and diabetic macular oedema[2]. Similar lesions can appear in kidneys. Endothelial cells cover the luminal side of blood vessels of all calibres, including the microscopic capillaries which are composed of basement membranes[3].

In both types of diabetes, patients, especially those with PDR, were found to have high serum VEGF-A concentrations. Furthermore, patients with higher serum VEGF-A were associated with macroalbuminuria (urinary albumin to creatinine ratio (ACR) >300 mg/g) and those with lower serum VEGF-A with microalbuminuria (urinary ACR: 30-300 mg/g)[4]. Indeed, the presence of a significant

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correlation between albuminuria and serum VEGF-A concentrations is similar to the findings that have been shown in a group of type 2 diabetic patients with serum creatinine concentrations of less than 2 mg/dl[5].

Several strategies have been developed in recent decades for DR screening, such as the non-mydriatic fundus camera and optical coherence tomography (OCT). Studies have determined the validity of these devices for detecting pre-proliferative / proliferative retinopathy and macular oedema[6,7], but no study has validated the use of serum VEGF-A and ACR for DR screening by comparing them to OCT. This study investigated the validity of serum VEGF-A and ACR by comparing them to the OCT technique for differentiating between diabetic no retinopathy and DR, and between proliferative and non-proliferative forms of DR.

SUBJECTS AND MATERIALS

Study groups

This cross-sectional study was conducted in 2017 at the Clinical Analysis Department, College of Pharmacy, Hawler Medical University. The study comprised of 164 diabetic patients: 30 patients with no retinopathy who served as the control group, 86 patients with non-proliferative diabetic retinopathy (NPDR), and 48 patients with PDR. Patients were referred to Layla Qasim Diabetic Center between November 2016 and October 2017 and asked to fill out a questionnaire. All patients were between 11 and 75 years of age.

All patients were diagnosed and evaluated by an ophthalmologist and classified according to the Early Treatment Diabetic Retinopathy Study criteria[8]. The study was approved by the Ethics Committee of the College of Pharmacy at the Hawler Medical University and verbal consent was obtained from all study participants.

Exclusion criteria

Patients were excluded from the study if they received intravitreal injections for at least three months prior to the start of the study, have undergone a vitrectomy, or have a history of chorioretinal abnormalities. Patients with a history of renal or liver impairment, malignancy, cardiovascular disease (recent myocardial infarction, stroke, peripheral artery disease), uncontrolled hypertension (≥140/90 mmHg), deep vein thrombosis and pulmonary embolism were also excluded from the study.

Table 1: Distribution of the study population by age, gender, type of DM, duration and type of treatment

Variables	Diabetic				*P*
	No retinopathy		Retinopathy		
	n	%	n	%	
Age (years)					<.001
<30	10	33.3	5	3.7	
30-44	5	16.7	10	7.5	
45-59	13	43.3	67	50.0	
60+	2	6.7	52	38.8	
Total	30	100.0	134	100.0	
Gender					.73[NS]
Female	18	60.0	85	63.4	
Male	12	40.0	49	36.6	
Total	30	100.0	134	100.0	
Type-II DM (compared to type-I)					.09[NS]
Type-I	15	50.0	45	33.6	
Type-II	15	50.0	89	66.4	
Total	30	100.0	134	100.0	
Duration of DM (years)					<.001
<5	15	50.0	9	6.7	
5-9	8	26.7	27	20.1	
10-14	6	20.0	32	23.9	
15-19	1	3.3	32	23.9	
20+	0	0.0	34	25.4	
Total	30	100.0	134	100.0	
Treated with insulin (solo or in combination with oral hypoglycemics) compared to oral hypoglycemics					.56[NS]
Oral hypoglycemic agent	13	43.3	66	49.3	
Insulin	17	56.7	68	50.7	
Total	30	100.0	134	100.0	

DM: diabetes mellitus; NS: not significant

Sample collection

Five millilitres of venous blood with minimal stasis were collected from each subject. Blood without anticoagulant was allowed to clot, and it was centrifuged for 15 minutes at 3000 rpm. Thereafter, the obtained sera were dispensed into eppendorf tubes and immediately frozen at -20 °C until tested.

Determination of serum VEGF-A was done by using enzyme-linked immunosorbent assay kit (MyBioSource; VEGF-A ELISA Kit, San Diego, CA 92195-3308, USA). At the same time, a urine sample was collected from each patient to test for urinary albumin and creatinine for estimation of albuminuria; normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR = 30-300 mg/g) and macroalbuminuria (ACR >300 mg/g).

Urinary creatinine was estimated using Creatinine Jaffe Gen.2 Kit (Roche Diagnostic, Germany, compensated, Ref: 05401755), and urinary albumin was estimated using Human Micro-Albuminuria Detection Kit Nephelometry (Ref: 32031007, Chem, 100.Genis, Italy).

Study protocol

Detailed information about each patient, including age, gender, duration of diabetes in years, type of diabetes, type of diabetic treatment, hypertension, and dyslipidaemia was recorded.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences version 22. A one-way analysis of variance was used to compare the means of the three groups. A post hoc test was used to determine where the significant differences occurred between the groups. A chi-square test of association was used to compare proportions between the groups. Logistic regression analysis was carried out with retinopathy as the dependent variable. Receiver operating characteristic (ROC) curve was plotted in order to estimate the cut-off value that provides the highest sensitivity and the highest specificity (knowing that when sensitivity increases, the specificity decreases). The highest Youden's index value (J = sensitivity+specificity-1) was used to estimate the cut-off value[9]. McNemar's test was used to determine if there are differences between the results of VEGF-A and ACR as screening test (whether positive or negative) compared to the results of the gold standard (OCT). $P \leq .05$ was considered statistically significant.

Table 2: The difference in mean VEGF-A and ACR by retinopathy

Study groups	n	(Mean+SD)	*P* (ANOVA)	LSD (Groups)	*P* (LSD)
VEGF (pg/ml)			<.001		
A) No retinopathy	30	(95.9 ± 59.8)		A X B	<.001
B) Non-proliferative	86	(269.1 ± 218.2)		A X C	<.001
C) Proliferative	48	(413.7 ± 301.3)		B X C	.001
ACR (mg/g)			0.003		
A) No retinopathy	30	(37.5 ± 71.5)		A X B	.012
B) Non-proliferative	86	(118.7 ± 166.9)		AX C	<.001
C) Proliferative	48	(159.2 ± 153.3)		B X C	.136
HbA1c %			0.429		
A) No retinopathy	30	(9.03 ± 1.9)		A X B	.570
B) Non-proliferative	86	(9.27 ± 2.1)		A X C	.213
C) Proliferative	48	(9.6 ± 2.4)		B X C	.347

VEGF-A: vascular endothelial growth factor A; ACR: albumin to creatinine ratio; ANOVA: one way analysis of variance; LSD: post hoc test

RESULTS

The total number of patients was 164. Their ages ranged from 11 to 75 years (mean: 52.1±13.6 years). The mean age of the diabetic patients with no retinopathy was 38.9±17.9 years, the mean age of the NPDR group was 55.4±9.9 years, and the mean age of the PDR group was 54.3±11.4 years.

Table 1 shows the baseline characteristics of study patients. Of the 164 diabetic patients, 30 were diagnosed diabetic with no retinopathy; 18 (60%) of them were females and 15 patients (50%) were type I diabetic. Furthermore, 17 patients of this group (56.7%) received insulin as a treatment. The second group consisted of 134 patients with diabetic retinopathy, 85 (63.4%) of them were females, 45 (33.6%) patients were type I diabetic and 68 (50.7%) patients received insulin as a treatment. These variables (gender, type of the diabetic and type of treatment) showed no statistically significant differences between the two groups ($P > .05$).

Table 3: Prevalence of albuminuria by retinopathy

Study groups	Albumin to creatinine ratio (ACR)						*P*
	Normal		Microalbuminuria		Macroalbuminuria		
	n	%	n	%	n	%	
No retinopathy	25	83.3	4	13.3	1	3.3	
Non-proliferative	38	44.2	37	43.0	11	12.8	<.001
Proliferative	8	16.7	33	68.8	7	14.6	

Only the age and diabetic duration showed statistically significant differences (*P*<.001) between the two groups. In diabetic with no retinopathy group, 10 patients (33.3%) were under 30 years of age and 29 (96.7%) were diabetic for less than 15 years, while in the diabetic retinopathy group, five patients (3.7%) were under 30 years of age and 68 (50.7%) patients were diabetic for less than 15 years.

The results of the pairwise comparisons in Table 2 indicate that the mean VEGF-A level were significantly lower in the group of diabetic patients with no retinopathy (95.9±59.8 pg/ml) than they were in NPDR group (269.1±218.2 pg/ml) and the PDR group (413.7±301.3 pg/ml).

There were significant differences between the mean ACR of the three groups (*P*=.003) as indicated by Table 2. The mean ACR of the group of diabetic patients with no retinopathy (37.5±71.5 mg/g) was significantly different (*P*=.012) from the mean ACR of the NPDR group (118.7±166.9 mg/g) and from the mean ACR of the PDR group (159.2±153.3 mg/g, *P*=.001). Even though the mean ACR of the PDR group was higher than the mean of the NPDR group, this difference was not significant (*P*=.136).

However, no statistically significant differences were detected between the mean HbA1c of the three groups (*P*=.429).

Table 3 shows that the prevalence of macroalbuminuria among the diabetic patients with no retinopathy (3.3%) was significantly lower (*P*<.001) than among the NPDR patients (12.8%) and the PDR patients (14.6%). The analysis was done by chi-square (X^2).

The results of the binary logistic regression analysis presented in Table 4 indicate that the higher the patient's age, the higher the probability of him or her developing retinopathy. The results also indicate a significant positive association between VEGF-A and retinopathy. No significant association was detected between hypertension and ACR with retinopathy.

Table 5 shows that the area under the ROC curve of VEGF-A (0.806) and the ROC area of ACR (0.790), when used as screening tests for DR, significantly differed from the midline area (*P*<.001). Regarding the screening for PDR, the area under the ROC curve of VEGF-A (0.656) and the area of ACR (0.647) significantly differed from the midline area (*P*=.003 and *P*=.005, respectively).

Table 4: Binary logistic regression analysis with retinopathy as the dependent variable

Covariates	B	*P*	OR	95% CI for OR	
				Lower	Upper
Age (years)		.005			
<40 (reference)					
40-49	1.806	.036	6.086	1.127	32.866
50-59	2.421	.005	11.262	2.076	61.089
≥ 60	3.764	.001	43.132	5.042	369.007
Hypertension	-0.136	.827	0.873	0.258	2.956
VEGF	0.009	.001	1.009	1.004	1.015
ACR		.090			
Normal <30 (reference)					
Microalbuminuria 30-300	1.274	.064	3.576	0.929	13.767
Macroalbuminuria >300	1.675	.141	5.339	0.574	49.684

VEGF: vascular endothelial growth factor; ACR: albumin to creatinine ratio; OR: odds ratio; CI: confidence interval

Table 6 shows the cut-off values and the validity measures for VEGF-A and ACR in screening for DR, and their values and validity measures for differentiating PDR from NPDR. The results and the validity of these tests significantly differed from OCT, which is considered the gold standard in DR detection. However, when these two tests were combined, the sensitivity increased to 91% and specificity decreased to 70%. The results did not differ significantly from OCT (*P*=.664) when they were used together for the diagnosis of DR. However, the sensitivity increased to 95.8% and specificity decreased to 31.4% (*P*<.001) when both tests were used to differentiate PDR from NPDR.

Table 5: ROC areas for VEGF and ACR as screening tests for the detection of DR, and as test for differentiating PDR from NPDR

Screening variables	Area	SE	*P*	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Screening for diabetic retinopathy					
VEGF	0.806	.034	<.001	0.739	0.873
ACR	0.790	.048	<.001	0.696	0.884
Screening for proliferative diabetic retinopathy					
VEGF	0.656	0.049	.003	0.560	0.753
ACR	0.647	0.048	.005	0.553	0.741

ROC: receiver operating characteristic; VEGF: vascular endothelial growth factor; ACR: albumin to creatinine ratio; DR: diabetic retinopathy; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; SE: standard error

Table 6: Cut-off values and validity parameters of VEGF and ACR as screening tests for the detection of DR, and as screening tests for differentiating PDR from NPDR

Tests	Cut-off value	Sensitivity	Specificity	PV+	PV-	Total agreement	*P*
Screening for retinopathy							
VEGF	164.7pg/ml	65.7	93.3	97.8	37.8	70.73	<.001
ACR	18.7mg/g	79.1	76.7	93.8	45.1	78.65	<.001
Combined tests		91.0	70.0	93.1	63.6	87.19	.664
Screening for proliferative retinopathy							
VEGF	225.8pg/ml	75.0	54.7	48.0	79.7	61.9	<.001
ACR	38.4mg/g	79.2	48.8	46.3	80.8	59.7	<.001
Combined tests		95.8	31.4	43.8	93.1	54.4	<.001

VEGF: vascular endothelial growth factor; ACR: albumin to creatinine ratio; DR: diabetic retinopathy; PDR: proliferative diabetic retinopathy; NPDR: non-proliferative diabetic retinopathy; PV+: positive predictive value; PV-: negative predictive value

DISCUSSION

The highly prevalent complications in chronic hyperglycaemia are several microvascular lesions: diabetic retinopathy, diabetic nephropathy, and diabetic polyneuropathy[10,11]. Previous studies have confirmed an association between these three microvascular lesions, and denoted that patients with diabetic polyneuropathy have a four times higher rate of DR and a two times higher rate of microalbuminuria, when compared to a control group[12,13].

The results of this study suggest that patients with PDR have a higher rate of developing nephropathy than patients with NPDR and diabetic patients with no retinopathy, as suggested by the prevalence of microalbuminuria among these three groups, which are 68.8%, 43%, and 13.3% respectively (see Table 3). This means that the more progressive form of retinopathy is associated with higher prevalence of kidney deterioration. Additionally, these results indicate that patients with DR are more likely to develop diabetic nephropathy, and that the kidney and retina may have similar risk factors for microvascular disease due to diabetes mellitus[14,15].

A strong predictor of retinopathy in diabetic patients was age, followed by VEGF-A. However, no significant association was found between hypertension and DR (see Table 4). This might be due to the original selection of our study sample, because we included only patients with well-controlled blood pressure. However, the results of a randomized clinical trial showed that a reduction of blood pressure to less than 140/90 mmHg was correlated with a reduction in the rate of progression of microvascular lesion in hypertension patients with diabetes mellitus[16]. Moreover, medical treatment of hypertension gives a protective effect, though only in the early stages of DR.

The independent effect of macro and microalbuminuria indicated a 5.3-fold and 3.5-fold increased risk of developing DR respectively (see Table 4). Although this effect was not statistically significant, it is in keeping with the findings by Pedro *et al*, which demonstrated that DR highly correlates with overt nephropathy, and that microalbuminuria is a clear risk factor for DR[17]. Other recent studies have shown that the mere presence of DR may put patients at risk for diabetic nephropathy[14,18].

In the present study, a high level of serum VEGF-A was demonstrated in DR and a significantly higher level in more progressive types of the disease (PDR) (see Table 2). This indicates that VEGF-A is an effective factor which induces neovascularization in more progressive forms of retinopathy, which is in agreement with findings from others studies[19,20]. Similarly, the ACR and microalbuminuria were significantly higher in more progressive forms of DR (Table 3). This finding is also in keeping with the results of other studies[21].

The surprise finding in this study is that there was no significant difference (*P*=.664) when screening for retinopathy among diabetic patients between using the gold standard OCT, on the one hand, and using the combination of the cut-off values for VEGF-A and ACR (164.7 pg/ml and 18.7 mg/g, respectively). According to the results of McNemar's test, the sensitivity and specificity of the approach using the combined cut-off values for VEGF-A and ACR were 91% and 70%, respectively. However, the results of using one of these biomarkers alone for the same purpose were significantly different from the OCT results (*P*<.001). Thus, they have poor diagnostic validity if used alone. Furthermore, the approach of using the combination of VEGF-A and ACR failed to differentiate between PDR and NPDR (Table 6).

We found no other studies that analysed the validity of these biomarkers by comparing them to OCT. This study used OCT in addition to ophthalmological examinations to detect retinopathy in diabetic patients. Several studies estimated the validity of some devices for the diagnosis of DR, and these are presented in a meta-analysis by Bragge *et al*. For example, the sensitivity and specificity of mydriasis as a diagnostic test for DR were calculated to be 84.5% and 88.6%,

respectively (the likelihood ratio of positive to negative was 7.41:0.17)[22].

Another cross-sectional observational study checked the eyes of 136 diabetic patients with suspected referable retinopathy (non-proliferative, proliferative, and macular oedema). Both the ophthalmological examination of the retina and OCT were used to detect retinopathy and macular oedema. The validity factors showed a sensitivity of 91.67% and specificity of 93.18%[7].

Based on the validity parameters of using the combination of serum VEGF-A and ACR with the total agreement value of 87.19 (Table 6), we can conclude that this approach can be used for screening and differentiating DR from diabetic patients with no retinopathy, after applying all exclusion criteria. It would be advisable to apply this approach in areas with low socioeconomic status because it is less costly than OCT; in case of negative results, patients would be referred to their physician for an OCT confirmation.

CONCLUSION

Compared to OCT, the combination of serum VEGF-A and urinary ACR provides reasonable diagnostic power for differentiating DR from diabetic patients with no retinopathy, although it demonstrates no significant validity for differentiating the disease progression (NPDR from PDR).

REFERENCES

1. Wong TY, Cheung CMG, Larsen M, Sharma S, Simo R. Diabetic retinopathy. Nat Rev Dis Primers 2016; 2:16012.
2. Cunha-Vaz, J, Ribeiro L, Lobo C. Phenotypes and biomarkers of diabetic retinopathy. Prog Retin Eye Res 2014; 41:90-111.
3. Jaffe EA. Cell biology of endothelial cells. Hum Pathol 1987; 18(3):234-239.
4. Abdel Aziz MY, Ben Gharbia O, el-Sayed Mohamed K, Muchaneta-Kubara EC, el Nahas AM. VEGF and diabetic microvascular complications. Nephrol Dial Transplant 1997; 12:1538.
5. Cha DR, Kim NH, Yoon JW, Jo SK, Cho WY, Kim HK, *et al*. Role of vascular endothelial growth factor in diabetic nephropathy. Kidney Int Suppl 2000; 77:S104-112.
6. Baeza M, Orozco-Beltran D, Gil-Guillen VF, Pedrera V, Ribera MC, Pertusa S, *et al*. Screening for sight threatening diabetic retinopathy using non-mydriatic retinal camera in a primary care setting: to dilate or not to dilate? Int J Clin Pract 2009; 63(3):433-438.
7. Azrak C, Baeza-Dıaz MV, Palazon-Bru A, Hernandez-Martınez C, Navarro-Navarro A, Martinez-Toldos JJ, *et al*. Validity of optical coherence tomography as a diagnostic method for diabetic retinopathy and diabetic macular edema. Medicine 2015; 94(38):1-5.
8. Early Treatment Diabetic Retinopathy Study design and Baseline Patient Characteristics. ETDRS report number 7. Ophthalmology 1991; 98(5 Suppl):741-756.
9. Bewick V, Cheek L, Ball J. Statistics Review 13: Receiver operating characteristic curves. Crit Care 2004; 8(6):508-512.
10. Agardh E, Agardh CD, Koul S, Torffvit O. A four-year follow-up study on the incidence of diabetic retinopathy in older onset diabetes mellitus. Diabet Med 1994; 11(3):273-278.
11. Cohen O, Norymberg K, Neumann E, Dekel H. Complication-free duration and the risk of development of retinopathy in elderly diabetic patients. Arch Intern Med 1998; 158(6):641-644.
12. Barr EL, Wong TY, Tapp RJ, Harper CA, Zimmet PZ, Atkins R, *et al*. Is peripheral neuropathy associated with retinopathy and albuminuria in individuals with impaired glucose metabolism? The 1999– 2000 AusDiab. Diabetes Care 2006; 29(5):1114-1116.
13. Jeng CJ, Hsieh YT, Yang CM, Yang CH, Lin CL, Wang IJ. Diabetic retinopathy in patients with diabetic nephropathy: Development and progression. PLoS One 2016; 11(8):e0161897.
14. Lee WJ, Sobrin L, Kang MH, Seong M, Kim YJ, Yi JH, *et al*. Ischemic diabetic retinopathy as a possible prognostic factor for chronic kidney disease progression. Eye 2014; 28(9):1119-1125.
15. Rodríguez-Poncelas A, Mundet-Tudurí X, Miravet-Jiménez S, Casellas A, Barrot-De la Puente JF, Franch-Nadal J, *et al*. Chronic kidney disease and diabetic retinopathy in patients with type 2 diabetes. PLoS One 2016; 11(2):e0149448.
16. Volpe M, Battistoni A, Savoia C, Tocci G. Understanding and treating hypertension in diabetic populations. Cardiovasc Diagn Ther 2015; 5(5):353-363.
17. Pedro RA, Ramon SA, Marc BB, Juan FB, Isabel MM. Prevalence and relationship between diabetic retinopathy and nephropathy, and its risk factors in the North-East of Spain, a population-based study. Ophthalmic Epidemiol 2010; 17(4):251-265.
18. Karlberg C, Falk C, Green A, Sjolie AK, Grauslund J. Proliferative retinopathy predicts nephropathy: A 25-year follow-up study of type 1 diabetic patients. Acta Diabetol 2012; 49(4):263-268.
19. Mahdy RA, Nada WM. Evaluation of the role of vascular endothelial growth factor in diabetic retinopathy. Ophthalmic Res 2011; 45(2):87-91.
20. Ahmed HM, Alsihlawi M, Abdulameer F. The relevance of serum level of VEGF in type 2 diabetic retinopathy. Kufa Medical Journal 2012; 15(3):106-113.
21. AlFehaid AA. Prevalence of microalbuminuria and its correlates among diabetic patients attending diabetic clinic at National Guard Hospital in Alhasa. J Family Community Med 2017; 24(1):1-5.
22. Bragge P, Gruen RL, Chau M, Forbes A, Taylor HR. Screening for presence or absence of diabetic retinopathy: A meta-analysis. Arch Ophthalmol 2011; 129(4):435-444.

Original Article

Can methemoglobin be the responsible agent of mortality and morbidity in carbon monoxide intoxications?

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ABSTRACT

Objective: Mortality in carbon monoxide (CO) intoxications is associated with the blood carboxy hemoglobin (COHb) levels. In some fatal intoxication cases, normal levels of CO revealed that other mechanisms may exist in intoxications and the follow-up shouldn't be based solely on COHb levels. We aimed to investigate the effect of methemoglobin (metHb) on the morbidity and mortality in CO poisoning.
Design: Retrospective cohort study
Setting: Department of Emergency Medicine, Konya Education and Research Hospital, Konya, Turkey
Subjects: One hundred and one patients with CO intoxication
Intervention: The laboratory parameters and demographic data of patients were recorded during admission and after six hours of monitoring. The patients were grouped separately according to cardiac affections (affected and non-affected) and types of therapy (hyperbaric oxygen therapy (HBOT) and normobaric oxygen therapy). The groups were compared according to demographic data and laboratory parameters.
Main outcome measure: Importance of metHB in CO intoxications
Results: The levels of lactate, COHb and metHb measured at the time of admission were significantly higher in the cardiac damage group (P=.009, P=.023 and P=.003, respectively). The lactate, COHb and creatine kinase levels measured during admission to ER were significantly higher in the HBOT group (P=.04, P<.001 and P=.003 respectively). The metHB value measured during admission was not statistically significant, although it was higher in the oxygen receiving group (P=.06).
Conclusion: In patients with cardiac damage, methemoglobinemia worsens hypoxia, and thus closely affects the morbidity and mortality together with COHb. Thus, the assessment of CO intoxications should be multidisciplinary and should be analyzed with measureable gases other than COHb, especially metHb, and therapy should be guided accordingly.

KEY WORDS: carbon monoxide intoxication, carboxy hemoglobin, emergency room, hyperbaric oxygen treatment, methemoglobin

INTRODUCTION

The gas which is held responsible for intoxications occurring as a result of burning of organic materials located in closed spaces such as house fires and exhaust leakages is mostly carbon monoxide (CO) gas[1]. The oxygen consumption associated with high temperatures, the carbon particles produced and other volatile toxic compounds which are formed depending on the type of the burning materials (*i.e.* hydrochloric acid and nitrogen oxide (NO)) may directly contribute to the toxic effect of the ambient gas mixture, although high quantities of CO produced is indicated as the primary cause of morbidity in the death of persons who are exposed to such gases[2,3].

While CO level of 25-50% in the environment causes serious toxicity, levels over 50% are lethal. The mortality in these cases is directly associated with the blood carboxy hemoglobin (COHb) levels[1]. However, in some subjects with mortality associated with CO intoxication, it has been observed that the COHb levels were quite under the toxic levels, and this suggested other factors which affect mortality. Some studies reported lethal hydrogen cyanide levels, as well as COHb levels which are non-lethal, in the

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intoxications that occurred due to the burning of polymers which contain nitrogen, and its relation with mortality has been discussed[4-7]. Another chemical compound whose association with mortality was discussed is methemoglobin (metHb). metHB is one of the abnormal forms of the hemoglobin molecule and is formed by the oxidation of the iron from the hemoglobin molecule from ferrous form (Fe^{+2}) to ferric form (Fe^{+3})[8]. metHb normally forms a very small part of the total hemoglobin (approximately 1%). However, if the metHb levels increase sufficiently to represent a significant part of total hemoglobin, then its oxygen carrying capacity decreases and leads to tissue hypoxia[9]. This in turn is manifested with central cyanosis, which may lead to lack of response to oxygen therapy and decrease in the oxygen supply[10,11]. Some studies indicate that the blood of putrefactive sacrifices contains significant amounts of metHb[12,13]. However, recently it has been shown that, especially in anemic patients, in cases of CO intoxication and also in similar cases, even a small increase in metHb may be significant, and that this affects the morbidity and mortality in association with especially high NO values[14,15].

However, there are few studies on compounds which produce metHb during fires and their role within the final lethal mechanism. In this study, we aimed to investigate the effect of metHb on the morbidity and mortality in CO intoxication, based on the assumption that COHb is not the only cause of CO intoxication.

SUBJECTS AND METHODS

Study groups and study design

This was a retrospective, cross-sectional, single-center study approved by our local ethics committee. The study was conducted in the emergency room of a tertiary education research hospital. The patients who were hospitalized to emergency toxicology intensive care and admitted to emergency room due to CO intoxication between Jan 2016- Dec 2017 were included in the study. Archived and electronically stored records of patients were accessed. Pregnant and breastfeeding patients, patients whose records could not be accessed, and patients under 18 years and over 90 years were excluded from the study.

The laboratory parameters (full blood count, biochemical data and blood gas) of 101 patients who were included, together with their demographic data, were recorded at admission and after six hours of monitoring. The patients were then grouped separately according to the cardiac affections (affected and non-affected) and types of therapy (hyperbaric oxygen therapy (HBOT) and normobaric oxygen therapy (NBOT)). The groups were compared according to the demographic data and laboratory parameters.

Table 1: General demographic and laboratory data

Demographic and Laboratory Features	Value (mean or frequency)
Age (years)	1.04±2.16
Gender	
Male	44 (43.6%)
Female	57 (56.4%)
Complaints	
Nausea-vomiting	54 (53.5%)
Dyspnea	3 (3%)
Headache	13 (12.9%)
Syncope	6 (5.9%)
Cardiac arrest	1 (1%)
Dizziness	8 (7.9%)
Palpitation	1 (1%)
Unconsciousness	2 (2%)
Laboratory	
Hemoglobin	13.98±0.25
pO_2	21 (IQR=14.75)
pCO_2	39.23±0.72
pCO_2 at 6th hour	41 (IQR=7.5)
Lactate	2.84±0.27
Lactate at 6th hour	1.50 (IQR=1.40)
Base excess	-1.92±0.47
Base excess at 6th hour	0.50 (IQR=2.55)
Carboxy hemoglobin	22.36±1.06
Carboxy hemoglobin at 6th hour	1.80 (IQR=3.90)
Methemoglobin	2.46±0.08
Methemoglobin at 6th hour	2.30±0.08
Troponin	0.08±0.03
Troponin at 6th hour	0.02 (IQR=0.07)
pH	7.37±0.01
pH at 6th hour	7.37±0.01
CK-MB	2.10±1.50
CK-MB at 6th hour	0.80 (IQR=1.20)
Presence of cardiac damage	10 (9.9%)
Treatment	
O_2 treatment	35 (34.6%)
Hyperbaric trearment	66 (65.4%)
Outcome	
Discharged	99 (98%)
Hospitalization	2 (2%)
Hospitalization time (day)	2.02±0.94

CK-MB: creatine kinase

Complete blood count and biochemical analysis

All biochemical tests, blood gas analysis, and complete blood counts (on venous blood) were analyzed using fully automated devices.

Statistical analysis

All statistical analyses were performed with the aid of SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA). Data distribution was evaluated using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean±SD and categorical variables as frequencies (percentages). The significance of each difference between continuous variables was explored

with the aid of the Independent Samples t-test or the Mann-Whitney U-test. The significance of each difference between categorical variables was compared using Pearson's Chi-squared test. A *P* value <.05 was considered to reflect statistical significance.

RESULTS

The demographic data of the 101 patients who were evaluated is summarized in Table 1. The median age of the patients was 41.04±2.16 years. The female/male ratio was 1.3/1. The most common emergency complaint was nausea and vomiting (53.5%). Ten patients (9.9%) had cardiac damage. While NBOT was administered to 34.6% of the patients, HBOT was administered to 65.4%. Most of the patients were discharged after treatment and two patients died.

The factors which played a role in the development of cardiac damage are summarized in Table 2. There was no difference between the groups in terms of age and gender. In terms of laboratory parameters, the levels of lactate, COHb and metHb measured at the time of admission to the emergency room (ER) were significantly higher in the cardiac damage group (*P*=.009, *P*=.023 and *P*=.003, respectively). According to the parameters measured at 6th hour, there were differences between the groups only in terms of COHb (*P*=.037).

The data of the factors which affect the types of treatment administered to patients are summarized in Table 3. There was no difference between the groups in terms of age, gender and termination. In terms of laboratory parameters, the lactate, hemoglobin and creatine kinase levels measured during admission to ER were significantly higher in the HBOT group (*P*=.04, *P*<.001 and *P*=.003 respectively). The metHb value measured during the admission was not statistically significant, although it was higher in the oxygen receiving group (*P*=.06).

DISCUSSION

Gas and smoke intoxication is one of most common intoxication causes for admission to ER. Firstly, CO gas was held responsible in almost all such types of intoxications. However, recent studies on CO intoxications indicated COHb levels lower than 5% in many patients affected by the gas, and this suggested that other types of gases may lead to clinic dysfunctions in such intoxications[16,17]. It is thought that all factors such as hypoxia, carbon dioxide narcosis, high temperature values, and production of other gases such as hydrochloric acid and NO are directly affecting the intoxication mechanism together with CO or alone. However, the publications available are quite limited and just a few are based on the data

Table 2: The comparison of groups according to cardiac affections

Demographic and laboratory features	Cardiac damage		*P*
	No (n=91)	Yes (n=10)	
Age (years)	44 (IQR=26.75)	27 (IQR=40)	.262
Gender			.744
Male	39 (42.9%)	5 (50%)	
Female	52 (57.1%)	5 (50%)	
Laboratory			
Hemoglobin	14.10 (IQR=3.03)	13.30 (IQR=6.10)	.896
pO_2	23 (IQR=14.88)	19.30 (IQR=19)	.708
pCO_2	41 (IQR=7.75)	42 (IQR=11)	.592
pCO_2 at 6th hour	42 (IQR=8)	40 (IQR=7.50)	.114
Lactate	2.10 (IQR=1.80)	4.50 (IQR=7.10)	.009
Lactate at 6th hour	1.50 (IQR=1.45)	1.40 (IQR=1.55)	.757
Base excess	-1.10 (IQR=3.68)	-2.90 (IQR=9.30)	.053
Base excess at 6th hour	0.45 (IQR=2.58)	0.80 (IQR=3.25)	.897
Carboxy hemoglobin	22.50 (IQR=11.53)	31 (IQR=18.40)	.023
Carboxy hemoglobin at 6th hour	2.10 (IQR=4.10)	0.80 (IQR=1.60)	.037
Methemoglobin	2.20 (IQR=1)	3 (IQR=1)	.003
Methemoglobin at 6th hour	2.10 (IQR=1.10)	2.90 (IQR=1.90)	.795
pH	7.38 (IQR=0.06)	7.36 (IQR=0.14)	.078
pH at 6th hour	7.37 (IQR=0.04)	7.38 (IQR=0.05)	.633
Glasgow coma scale	15 (IQR=0)	15 (IQR=1)	1.000
Treatment			.158
O_2 treatment	34 (37.4%)	1 (10%)	
Hyperbaric trearment	57 (62.6%)	9 (90%)	
Outcomes			.010
Discharged	90 (98.9%)	9 (90%)	
Hospitalization	1 (1.1%)	1 (10%)	
Hospitalization time (day)	1 (IQR=0)	1 (IQR=1)	.085

Table 3: Distribution of data according to treatment options

Demographic and laboratory features	Treatment options		*P*
	NBOT (n=35)	HBOT (n=64)	
Age (years)	42.08±18.75	39.06±17.36	.423
Gender			.529
Male	17 (48.5%)	27 (42.2%)	
Female	18 (51.5%)	37 (57.8%)	
Outcomes			.298
Discharged	34 (97.2%)	63 (98.4%)	
Hospitalization	1 (2.8%)	1 (1.6%)	
Laboratory			
Hemoglobin	42.08 ± 18.75	39.06 ± 17.36	.911
pO_2	24 (IQR = 18.75)	21 (IQR = 13.50)	.052
pCO_2	40.54 ± 6.18	39.18 ± 8.81	.428
pCO_2 at 6th hour	43 (IQR = 7.50)	41 (IQR = 9)	.148
Lactate	1.70 (IQR = 1.85)	2.25 (IQR = 2.13)	.040
Lactate at 6th hour	1.30 (IQR = 1.05)	1.50 (IQR = 1.63)	.207
Base excess	-1.70 (IQR = 2.80)	-1.15 (IQR = 4.20)	.332
Carboxy hemoglobin	16 (IQR = 8.05)	26 (IQR = 10.85)	<.001
Carboxy hemoglobin at 6th hour	2.70 (IQR = 3.60)	1.55 (IQR = 3.90)	.170
Methemoglobin	2.67 ± 0.57	2.37 ± 0.83	.060
Methemoglobin at 6th hour	2.39 ± 0.69	2.10 ± 0.74	.795
Troponin	0.04 (IQR = 0.07)	0.01 (IQR = 0.04)	.261
Troponin at 6th hour	0.03 (IQR = 0.08)	0.01 (IQR = 0.06)	.256
pH	7.38 ± 0.07	7.37 ± 0.68	.659
pH at 6th hour	7.37 ± 0.03	7.37 ± 0.38	.694
CK-MB	0.30 (IQR = 0.70)	0.90 (IQR = 1.43)	.003

NBOT: normobaric oxygen therapy; HBOT: hyperbaric oxygen therapy; CK-MB: creatine kinase

of the affected individuals[2]. Taking into consideration these data, we researched that the responsible factor for morbidity and mortality in CO intoxication is not COHb, and that metHB may play an active role in this process.

The most important role of hemoglobin in the circulatory system is to carry oxygen. The structure of hemoglobin incorporates 4 heme proteins which are bounded with Fe^{+2} ions, and the oxygen carrying capacity is at its utmost level while it is in this status[18]. The affinity of CO, which consists of not well-burned carbon, to hemoglobin is 240 times its affinity to oxygen, and thus COHb which occurs in intoxication observed in fires is the most important gas which is held responsible for mortality[19]. However, in a burning environment, there are many other toxic substances and gases other than CO which may be lethal and most of them interact with heme protein[20]. One of these gases is NO gas which comes from burning plastics[15]. It is well known that high temperature burning of fossil combustibles leads to the collective formation of miscellaneous NOs known as nitros, such as NO and nitrogen dioxide. Such nitros gases occur in motors also due to nitrogen and by means of oxidation of the nitrogen which is connected to the fuel from the burning air. They also occur in gases caused by coal fires and non-explosive cesspits. NO, which occurs in case of intoxications due to the fires and which is more powerful than carbon dioxide, is absorbed through lungs and it is bound to hemoglobin with a very high affinity to form nitroxyl hemoglobin[17,21]. Nitroxyl hemoglobin oxidizes Fe^{+2} to Fe^{+3} and causes the hemoglobin to be transformed into metHb[22,23].

metHb is one of the abnormal forms of hemoglobin molecule and is created due to the oxidation of the iron from the hemoglobin molecule from Fe^{+2} to Fe^{+3}[8]. metHb is found in circulation as a result of being exposed to miscellaneous oxidant stresses; however, it represents a very small part of the total hemoglobin[12]. In normal healthy adults, endogenous mechanisms protect the tissues against oxidative stress and ensure that metHb levels are lower than 1%. In cases of increase in oxidation which cannot be overcome by these protective mechanisms, the metHb levels increase[24]. If the metHb levels increase so as to represent a significant part of the total hemoglobin, the oxygen carrying capacity of hemoglobin decreases and leads to functional anemia together with tissue hypoxia[9]. This in turn presents itself with central cyanosis, which may lead to lack of response to therapy and decrease in the oxygen supply[10,11]. Thus, although methemoglobinemia is a rare dysfunction, it should always be taken into consideration in the differential diagnosis of cyanosis patients[25]. Studies indicating the role of metHb in gas and smoke intoxications in the physiopathologic process are quite limited and in

general, they are just a case presentation. In one such case of intoxication from exhaust gas, the cause of death was indicated as CO intoxication; however, it has been determined that the COHb levels of the patients were not lethal. In the case of patients who did not present any other toxicological findings, the writers found an unusual metHb level and claimed that the death may be associated with developing hypoxia[26]. Again, in another study[27], the metHb levels of five patients from 32 victims of a fire environment were between 13-35.7% and the hydrogen cyanide values were 3.8-9 mg/dl, whereas metHb values from the other cases were found between 0.1-11.4%. The writers thought that preservation of blood and the vicinity of the deceased victims to windows during the fire may affect the metHb and COHb levels. They performed a correlation analysis in order to minimize error margins and found the best match between variables to be that between COHb and metHb.

Similar findings were confirmed in the studies conducted by Seto *et al*[28] and Katsumata[29]. According to Katsumata[29], heat denaturation was considered as the main reason for metHb production. In his study, while metHb levels which present negligible variations and high COHb levels were determined in the victims of urban gas intoxication, the victims of exhaust gas intoxication presented had higher levels of both CoHb and metHb. In some studies, it is reported that the post mortem decrease of metHb levels occurs as a result of reduction of metHb with the in-cell enzymatic reactions to hemoglobin and it continues a while after death[30]; and in vitro studies where factors such as hemolysis, freezing, melting, rotting and heat play a role reported that metHb levels increased post mortem[31]. However, the blood used in these studies were obtained from cadavers, so lack of information about the time spent by the victim in the burning environment and preservation conditions of blood lead to some amount of doubt. The blood samples used in our study were not post mortem and were collected from living patients. The samples collected at the arrival of the patient and at six hours after arrival were immediately analyzed.

The heart is one of the most vital organs which is affected by CO intoxications. The myocardial damage which occurs due to acute intoxications may be determined biochemically by the increase of cardiac markers such as phosphocreatine kinase and troponin. Miscellaneous studies indicated that troponin is the most important marker to decide the starting of HBOT and to show the cardiac damage in CO intoxication. The hypoxia which occurs together with increase in COHb levels may cause ventricular arrhythmias[32]. HBOT is one of the most efficient therapy methods used for CO intoxications[33]. It may be administered normobaric or hyperbaric. It is advised to be administered in general in the acute phase of intoxication and within the first six hours if possible[34,35]. Hampson *et al*[36] reported that clinical recovery is possible with NBOT, even in cases of loss of conscience due CO intoxication. In our study, in line with the literature, creatine kinase and troponin levels of the cardiac damage group were increased. In the cardiac damage group and especially during the acute period, we determined a significant correlation between COHb and metHb, since the metHb levels and COHb levels increased simultaneously. Moreover, we observed a significant improvement in both COHb and metHb levels after HBOT therapy.

CONCLUSION

In conclusion, in cases of patients where cardiac damage is especially considered, methemoglobinemia worsens hypoxia and thus closely affects the morbidity and mortality together with COHb. The oxygen and hyperbaric therapy administered to these patients has fewer benefits because methemoglobinemia is ignored. Thus, the assessment of CO intoxications should be multidisciplinary and should be analyzed with measurable gases other than COHb, especially metHb, and the therapy option should be guided accordingly.

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REFERENCES

1. Bleecker ML. Carbon monoxide intoxication. Handb Clin Neurol 2015; 131:191-203.
2. Alarie Y. Toxicity of fire smoke. Crit Rev Toxicol 2002; 32(4):259-289.
3. Alarie Y, Anderson RC. Toxicologic classification of thermal decomposition products of synthetic and natural polymers. Toxicol Appl Pharmacol 1981; 57(2):181-188.
4. Grabowska T, Skowronek R, Nowicka J, Sybirska H. Prevalence of hydrogen cyanide and carboxyhaemoglobin in victims of smoke inhalation during enclosed-space fires: A combined toxicological risk. Clin Toxicol (Phila) 2012; 50(8):759-763.
5. Chaturvedi AK, Smith DR, Canfield DV. Blood carbon monoxide and hydrogen cyanide concentrations in the fatalities of fire and non-fire associated civil aviation accidents, 1991-1998. Forensic Sci Int 2001; 121(3):183-188.
6. Ishii A, Seno H, Watanabe-Suzuki K, Suzuki O, Kumazawa T. Determination of cyanide in whole blood by capillary gas chromatography with cryogenic oven trapping. Anal Chem 1998; 70(22):4873-4876.

7. Ferrari LA, Arado MG, Giannuzzi L, Mastrantonio G, Guatelli MA. Hydrogen cyanide and carbon monoxide in blood of convicted dead in a polyurethane combustion: A proposition for the data analysis. Forensic Sci Int 2001; 121(1-2):140-143.
8. Nagababu E, Rifkind JM. Reaction of hydrogen peroxide with ferrylhemoglobin: Superoxide production and heme degradation. Biochemistry 2000; 39(40):12503-12511.
9. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: A retrospective series of 138 cases at 2 teaching hospitals. Medicine (Baltimore) 2004; 83(5):265-273.
10. Chui JS, Poon WT, Chan KC, Chan AY, Buckley TA. Nitrite-induced methaemoglobinaemia - Aetiology, diagnosis and treatment. Anaesthesia 2005; 60(5):496-500.
11. Johnson D. Perioperative methemoglobinemia. Can J Anaesth 2005; 52(7):665-668.
12. Reay DT, Insalaco SJ, Eisele JW. Postmortem methemoglobin concentration and their significance. J Forensic Sci 1984; 29(4):1160-1163.
13. Blackmore DJ. Interpretation of carbon monoxide levels found at postmortem, In: B. Ballantyne, editors. Forensic Toxicology, John Wright and Sons: Bristol, 1974, p.114-120.
14. Hare GMT, Mu A, Romaschin A, Tsui AKY, Shehata N, Beattie WS, *et al*. Plasma methemoglobin as a potential biomarker of anemic stress in humans. Can J Anaesth 2012; 59(4):348-356.
15. Katsumata Y, Aoki M, Oya M, Suzuki O, Yada S. Simultaneous determination of carboxyhemoglobin and methemoglobin in victims of carbon monoxide intoxication. J Forensic Sci 1980; 25(3):546-549.
16. Atkinson P, Langlois NE, Adam BJ, Grieve JH. Suicide, carbon dioxide, and suffocation. Lancet 1994; 344(8916):192-193.
17. deRoux SJ. Suicidal asphyxiation by inhalation of automobile emission without carbon monoxide intoxication. J Forensic Sci 2006; 51(5):1158-1159.
18. Umbreit J. Methemoglobin--it's not just blue: A concise review. Am J Hematol 2007; 82(2):134-144.
19. Wu PE, Juurlink DN. Carbon monoxide intoxication. CMAJ 2014; 186(8):611.
20. Naples R, Laskowski D, McCarthy K, Mattox E, Comhair SA, Erzurum SC. Carboxyhemoglobin and methemoglobin in asthma. Lung 2015; 193(2):183-187.
21. Laney RF, Hoffman RS. Methemoglobinemia secondary to automobile exhaust fumes. Am J Emerg Med 1992; 10(5):426-428.
22. Ryter SW, Otterbein LE, Morse D, Choi AMK. Heme oxygenase/carbon monoxide signaling pathways: Regulation and functional significance. Mol Cell Biochem 2002; 234-235(1-2):249-263.
23. Maines MD. The heme oxygenase system: A regulator of second messenger gases. Annu Rev Pharmacol Toxicol 1997; 37:517-554.
24. Anderson ST, Hajduczek J, Barker SJ. Benzocaine-induced methemoglobinemia in an adult: Accuracy of pulse oximetry with methemoglobinemia. Anesth Analg 1988; 67(11):1099-1101.
25. Jaffe ER, Hultquist DE. Cytochrome b5 reductase deficiency and enzymopenic hereditary methemoglobinemia. In: Scriver CR, Beaudet AL, Sly WS, editors. The Metabolic and Molecular Basis of Inherited Disease. 7th ed. McGraw-Hill: New York; 1995, p. 2267-80.
26. Vevelstad M, Morild I. Lethal methemoglobinemia and automobile exhaust inhalation. Forensic Sci Int 2009; 187(1-3):e1-5.
27. Ferrari LA, Giannuzzi L. Assessment of carboxyhemoglobin, hydrogen cyanide and methemoglobin in fire victims: A novel approach. Forensic Sci Int 2015; 256:46-52.
28. Seto Y, Kataoka M, Tsuge K. Stability of blood carbon monoxide and hemoglobins during heating. Forensic Sci Int 2001; 121(1-2):144-150.
29. Katsumata Y, Aoki M, Sato K, Oya M, Yada S, Suzuki O. A simple spectrophotometric method for the determination of carboxyhemoglobin in blood. Forensic Sci Int 1981; 18(2):175-179.
30. Rodkey FL, O'Neal JD. Effects of carboxyhemoglobin on the determination of methemoglobin in blood. Biochem Med 1974; 9(3):261-270.
31. Wallace KL, Curry SC. Postcollection rise in methemoglobin level in frozen blood specimens. J Toxicol Clin Toxicol 2002; 40(1):91-94.
32. Yurtseven S, Arslan A, Eryigit U, Gunaydin M, Tatli O, Ozsahin F, *et al*. Analysis of patients presenting to the emergency department with carbon monoxide intoxication. Turk J Emerg Med 2015; 15(4):159-162.
33. Hardy KR, Thom SR. Pathophysiology and treatment of carbon monoxide intoxication. J Toxicol Clin Toxicol 1994; 32(6):613-629.
34. Gorman DF, Clayton D, Gilligan JE, Webb RK. A longitudinal study of 100 consecutive admissions for carbon monoxide intoxication to the Royal Adelaide Hospital. Anaesth Intensive Care 1992; 20(3):311-316.
35. Gorman DF, Runciman WB. Carbon monoxide intoxication. Anaesth Intensive Care 1991; 19(4):506-511.
36. Hampson NB. Hyperbaric oxygen: A plea for uniform nomenclature. Undersea Hyperb Med 1999; 26(4):267.

Original Article

Is it possible to estimate the mortality rate of Fournier Gangrene with new parameters?

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ABSTRACT

Objective: The aim of the study was to compare currently used parameters and a new parameter platelet distribution width (PDW) to assess its potential value in estimating mortality in patients with Fournier gangrene.
Design: Retrospective study
Setting: Tepecik Training and Research Hospital, Izmir, Turkey
Subjects: Eighty-nine patients diagnosed with Fournier gangrene between January 2006 and March 2017 were included in this study.
Interventions: The two groups of patients, survivors and non-survivors, were compared with regard to the demographic data of patients, laboratory parameters, Age Charlson Comorbidity Index (ACCI), Uludag Fournier's Gangrene Severity Index (UFGSI), Fournier's Gangrene Severity Index (FGSI), Simplified Fournier's Gangrene Severity Index (SFGS), the neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio, red cell distribution width (RDW) and PDW.
Main outcome measures: Mortality rate of Fournier Gangrene
Results: There was a statistically significant correlation between mortality and ACCI, UFGSI, FGSI, SFGS, NLR and RDW. Advanced age, low calcium level, hemoglobin, haematocrit, bicarbonate levels and high levels of blood urea nitrogen were found to be significant factors for mortality ($P<.05$).
Conclusions: Our results revealed that ACCI, UFGSI, FGSI, SFGS, NLR and PDW are reliable predictors of mortality in patients with Fournier gangrene. Simple to calculate parameters such as SFGSI, NLR and PDW are helpful in predicting mortality in daily practice.

KEY WORDS: acute renal failure, Fournier Gangrene, mortality, new parameters, platelet distribution width

INTRODUCTION

The first real investigations of Fournier's gangrene (FG) were carried out by Baurienne in 1764, and the disease was defined as a rapidly progressing necrotizing fasciitis in the perianal and genital area[1]. Despite advances in medical and surgical treatment and intensive care over the centuries, the mortality rate of FG is still 7-30%[2-5]. The Fournier Gangrene Severity Index (FGSI)[2], Uludag FGSI (UFGSI)[3], and Age-Adjusted Charlson Comorbidity Index (ACCI)[4] are all used to calculate the prognosis of this life-threatening disease. These indices examine 9, 11 and 19 parameters, respectively. The FGSI system is based on nine scores for each parameter, whereas UFGSI includes the age of the patients and the extent of the disease in addition to those nine. While, FGSI and UFGSI cannot be generally applied at the bedside due to their complexity, ACCI[6] is simpler to use, although its calculation takes a significant amount of time. These limitations motivate researchers to find faster methods that use basic parameters to estimate mortality[3,4,7,8].

According to the literature, a simplified Fournier's Gangrene Severity Index (SFGSI)[5] measuring neutrophil-lymphocyte ratio (NLR)[9,10], platelet-lymphocyte ratio (PLR)[9], magnesium levels[8] and red cell distribution width (RDW) has previously been used to estimate mortality in FG. However, the use of platelet distribution width (PDW) in predicting the mortality rate of FG has not been recorded until now. The aim of this study was to evaluate factors impacting

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the survival of patients with FG and compare various indices and parameters that are currently used to estimate it. In addition, a new method, PDW, was analyzed to assess its potential value in estimating mortality.

SUBJECTS AND METHODS

The patients with FG between January 2006 - April 2017 at Tepecik Training and Research Hospital were retrospectively examined. Those who were operated due to perianal, perineal and genital necrotised soft tissue infection were included in the study, and patients who had solitary abscess without necrotised soft tissue infection were excluded. Patient records were obtained from the electronic registry system with the approval of the local ethics committee. Duration of symptoms (from the onset of symptoms to arrival at hospital), clinical parameters, co-morbidities, demographics, laboratory test results, renal insufficiency, blood transfusions and mortality in hospital were all recorded. Also, ACCI, SFGSI, NLR and PLR scores at the time of hospital admission were calculated. RDW and PDW values were obtained from a complete blood count. All patients received liquid electrolyte support and broad-spectrum intravenous antibiotics, as well as extensive surgical debridement to reach the bleeding healthy tissue in the first 24 hours of their admission. Antibiotic therapies were rearranged after gaining the first culture antibiogram results.

The ACCI was calculated by adding the separate scores for 19 medical conditions and by adding 1 to the index for each decade after the age of 50. SFGSI is measured as the total of potassium, creatinine and hematocrit scores from the FGSI parameters.

We defined moderate acute renal failure, one of the ACCI parameters, as slightly increased serum urea and creatinine levels, and severe acute renal failure as either an increase in serum creatinine levels of at least one and a half times the normal values or symptoms leading to immediate dialysis. The NLR and PLR were obtained by dividing the absolute neutrophil count or the absolute platelet count respectively by the absolute lymphocyte count. The PDW and RDW indices were based on routine laboratory blood count analysis. Patients were divided into two groups, survivors and non-survivors. Mortality was defined as disease-related death during the hospital stay. Clinical and laboratory findings were evaluated in terms of mortality. On the other hand, FGSI, UFGSI, ACCI, SFGSI, NLR, PLR, RDW and PDW were evaluated for mortality.

Statistical analysis

Descriptive statistics were presented as mean±standard deviation for variables with normal distribution, median (min-max) for variables without normal distribution and numbers (%) for categorical variables. Relevance of continuous numerical variables to normal distribution was tested by Kolmogorov-Smirnov and Shapiro Wilk normality tests, and homogeneity of group variance was tested by Levene test.

Student's t test was used for numerical variables in the groups when parametric test hypothesis was provided. When parametric test hypothesis was not provided, Mann-Whitney U test was used. Categorical variables were compared using Pearson chi-square and Fisher Exact Test when appropriate.

The cut-off values of UFGSI, FGSI, ACCI, SFGSI, NLR and PDW for discrimination between the groups were determined using receiving-operator characteristic analysis. For each value, the sensitivity, specificity and area under curve for each outcome were studied.

First type error probability for all tests were determined as α=0.05. Statistical analysis was performed by using R Project 3.2.5 and Med Calc 17.9.7 Trial.

Table 1: Distribution of comorbidities

Comorbidities	Survivors n(%) (n=69)	Non-survivors n(%) (n=20)	*P*
DM	31 (44.9)	13 (65.0)	.114[1]
HBP	19 (27.5)	7 (35.0)	.518[1]
CHD	11 (15.9)	8 (40.0)	.030[2]
ARF	5 (7.2)	7 (35.0)	.004[2]
CRF	5 (7.2)	2 (10.0)	.652[2]
Any Tumor	4 (5.8)	5 (25.0)	.025[2]
COPD	7 (10.1)	3 (15.0)	.688[2]
CVD	1 (1.4)	4 (20.0)	.008[2]

[1]Pearson Chi-Square Test; [2]Fisher-Exact Test
DM: diabetes mellitus; HBP: high blood pressure; CHD: coronary heart disease; ARF: acute renal failure; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease

Table 2: Comparison of prognostic parameters in terms of mortality

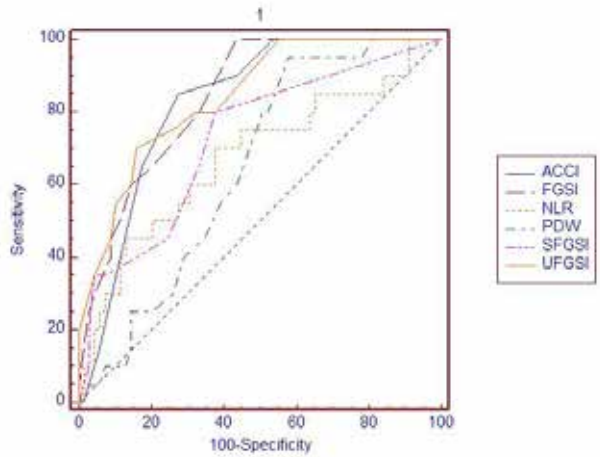
Index and parameters	Survivors (n=69) Median (Min-Max)	Non-survivors (n=20) Median (Min-Max)	*P**
NLR	10.79 (0.75-177.0)	16.51(2.78-130.0)	.019
PLR	210.0 (23.3-640.0)	264.0 (13.0-1620.0)	.326
PDW	17.1(15.8-20.4)	17.3 (16.4-20.8)	.047
RDW	14.4 (11.7-151.0)	15.8 (13.3-24.6)	.082
FGSI	4.0 (0-15)	8.5 (5-17)	<.001
UFSGI	7 (1-18)	13 (7-24)	<.001
SFGSI	0 (0-9)	2 (0-9)	.001
ACCI	3 (0-11)	6 (3-9)	<.001

*Mann-Whitney U Test
FGSI: Fournier's Gangrene Severity Index; UFGSI: Uludag Fournier Gangrene Severity Index; ACCI: Age Charlson Comorbidity Index; SFGSI: Simplified Fournier's Gangrene Severity Index; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; RDW: red cell distribution width; PDW: platelet distribution width

Table 3: Receiving-operator characteristic results

Variables	Cut off	AUC (95% CI)	Sensitivity	Specificity	*P*
UFGSI	10	0.842 (0.749-0.910)	70	84.06	.0001
FGSI	4	0.841 (0.748-0.910)	100	56.52	.0001
ACCI	4	0.826 (0.731-0.898)	85	72.46	.0001
SFGSI	0	0.725 (0.621-0.815)	80	62.32	.0012
NLR	13	0.672 (0.565-0.768)	70	62.32	.0175
PDW	16.8	0.646 (0.537-0.744)	95	42.03	.0472

AUC: area under the ROC curve; CI: confidence interval; FGSI: Fournier's Gangrene Severity Index; UFGSI: Uludag Fournier Gangrene Severity Index; ACCI: Age Charlson Comorbidity Index; SFGSI: Simplified Fournier's Gangrene Severity Index; NLR: neutrophil lymphocyte ratio; PDW: platelet distribution width



RESULTS

In total, 103 patient files were examined. Eighty-nine patients were included in the study. Fourteen patients who had localized abscess in anorectal or urogenital region without necrotized soft tissue infection were excluded. The mean age was 57 years (range: 27-86 years) with 58 male (65.2%) and 31 (34.8%) female patients. Twenty of the 89 patients (22.5%) died. The mean age of the survivors (53.9±13.57 years) was significantly lower than that of the non-survivors (67.6±11.52 years, *P*<.001). There was no statistical correlation between mortality and gender (*P*>.05). Diabetes mellitus (DM) is the most frequently seen comorbidity with FG patients (49.4%, n=44). However, DM was not observed to be a factor affecting mortality in our study (*P*=.114). From all the comorbidities examined, presence of a tumor, acute renal failure, cerebrovascular disease and coronary artery disease were associated with mortality. Comorbidities are summarized in Table 1. The median admission time (from the onset of symptoms to arrival at hospital) was 6 days (range: 1-30 days) and a comparison of the survivors' median admission time (4 days, range: 1-19 days) with that of the non-surviving group (7 days, range: 3-30 days) shows that surviving patients applied to the hospital earlier (*P*=.011). Microbiological analysis of the wound cultures examined were most commonly polymicrobial (n=54, 60.7%). In our study, microorganisms isolated were *E. coli, K. pneumoniae, Enterococci, Streptococci, Staphylococci* and *P. aeruginosa*, respectively.

A statistically significant difference was found between FGSI, UFGSI, ACCI, SFGSI, NLR, PDW and mortality in all prognostic parameters and scores. Table 2 shows the association between prognostic parameters and mortality. Table 3 shows the cutoff value, sensitivity and specificity. A significant relation between blood urea nitrogen (BUN), blood calcium level, hemoglobin, hematocrit, bicarbonate and PDW levels were observed from analyzed laboratory tests. Table 4 shows the correlation between laboratory parameters and mortality.

Table 4: Comparison of laboratory parameters for survivors and non-survivors

Laboratory parameters	Survivors (n=69)	Non-survivors (n=20)	*P*
Glucose			
Median(Min-Max)	149(45-617)	156(63-538)	.926[1]
Sodium			
Median(Min-Max)	135(121-187)	133.5(123-150)	.647[1]
Potassium			
Median(Min-Max)	4.2(3.0-6.1)	4.2(3.0-5.5)	.988[1]
BUN			
Median(Min-Max)	38(13-252)	86(22-313)	<.001[1]
Serum creatinine			
Median(Min-Max)	1.0(0.6-6.1)	1.6(0.6-3.7)	.096[1]
WBC			.783[1]
Median(Min-Max)	15.6(2.3-42.0)	15.2(5.4-32.3)	
Chlorine			.713[2]
Mean±SD	99.23±5.405	99.80±8.004	
Serum Calcium			<.001[2]
Mean±SD	8.84±0.621	7.84±0.795	
Hemoglobin			.029[2]
Mean±SD	11.90±2.289	10.64±2.061	
Haematocrit (%)			.027[2]
Mean±SD	35.81±6.593	32.08±6.433	
Serum Bicarbonate			<.001[1]
Median(Min-Max)	22.8(18.0-26.4)	17.95(13.0-21.0)	

[1]Mann-Whitney U Test; [2]Student's t Test
SD: standard deviation; WBC: white blood cell; BUN: blood urea nitrogen

DISCUSSION

In this study, we examined the predictors that have been claimed to be efficient to measure mortality rate in FG patients at the time of admission to the hospital with ease and high accuracy. Also, availability of RDW index in mortality prediction of patients with FG was investigated. The mortality rate in our study of 89 patients treated in our clinic over a ten-year period was 22.5%, and this rate is consistent with the literature[4,8,9,11].

Advanced age[12], DM[13], hypertension, congestive heart failure, renal failure, coagulopathy[14] and malignancy[15] are reported as the causes of death in patients with FG. However, Corcoran *et al* and Erol *et al* did not find any comorbid conditions to be significantly associated with mortality[16,17]. Although DM was the most encountered predisposing factor, it did not affect the outcome of patients in our study. However, we found that advaned age, malignancy, coronary artery disease and acute renal failure were risk factors associated with mortality. Laboratory parameters such as hematocrit, hemoglobin, serum albumin, BUN, blood creatinine, bicarbonate, lactate and calcium were affirmed as prognostic factors in some studies[2,12,16]. In the current study, we found that high BUN levels, low calcium, bicarbonate, hematocrit and hemoglobin levels were related with mortality.

In literature, it is shown that extended time between onset of symptoms to hospital admission is associated with poor prognosis[11,18]. Along with other studies, we did find the duration of symptoms as a major predictor for mortality[19,20].

Recently, some studies have shown that acute renal failure (ARF) increases mortality[11,14,21,22], while another study contradicts this result[16]. However, in FG literature arguing that ARF correlates with mortality, only Martinschek *et al*[22] define ARF with serum creatinine levels of >1.5 g/dl or <500 cc/day urine output. On the other hand, Kuo *et al*[21] define it as a progressive increase in the value of serum creatinine level and BUN. Thus, the definitions are different in the two publications, and objective values are mentioned in just one of them. Ronco *et al*[23] created a new diagnostic and classification system in 2001 to try to address this confusion and encourage multi-center studies that could be compared objectively. In 2012, the current internationally used Kidney Disease Improving Global Outcomes guidelines (KDIGO) were developed by blending various criteria[24]. According to KDIGO guidelines, the criteria for ARF are 0.3 mg/dl increase in serum creatinine level within 48 hours; at least a 1.5-fold increase in creatinine level in comparison to the normal values; and urine output that remains <0.5 ml/kg/h in the last 6-12 hours. These new KDIGO criteria differ from ARF defined in the FG literature. However, we cannot find use of new ARF criteria in the FG literature. Considering that mortality rates depend on the degree of damage and that ARF is defined in hours/days, we believe there should be a revision of this definition of ARF for scoring systems like FGSI, UFGSI, SFGSI and ACCI, which are used to predict mortality at the time of admission.

Roghmann *et al* find classic scoring systems such as FGSI, UFGSI and ACCI are useful for predicting mortality in patients with FG[4]. While Erol *et al* find Charlson Comorbidity index and FGSI useful[17], Tuncel *et al* assert only UFGSI is useful[12]. In the present study, we find that classic scoring systems like FGSI, UFGSI and ACCI may be used for predicting mortality. When the literature about FG is reviewed, threshold for FGSI was reported between ≥4 and 11, for UFGSI was between ≥5 and 9, for ACCI was ≥4[2-4]. In the present study, threshold for FGSI, UFGSI and ACCI was 4, 10 and 4 respectively. In addition, SFGSI that reproduced by FGSI was >2 in the original study. It was >0 according to our study results. We conclude that all these different threshold values may stem from different definitions of ARF. We consider that ARF definition that we used for FG in the literature should be universal to compare the literature results correctly.

In the present study, UFGSI is the best scoring system for predicting mortality in patients with FG. Due to the criticisms brought against the scoring systems (FGSI, UFGSI and ACCI) reviewed above and their time-consuming nature, researchers have recently focused on developing new and more practical scoring systems like NLR, PLR, RDW[5,7,9,10]. There has not been sufficient evaluation of these new methods in the literature yet. According to the present study, NLR is adequate for predicting the mortality of FG. PDW, a previously less-studied parameter for evaluation of mortality in FG, emerged as a reliable predictor of mortality in FG patients in the present study as well. The cut-off value for PDW was 16.8%. For this value, a sensitivity of 95% and a specificity of 42.03% were calculated.

CONCLUSION

Simple parameters such as SFGSI, NLR and PDW are easy to calculate and they are helpful in predicting mortality in FG patients. Meanwhile, PDW is seen as a new parameter which can predict mortality of patients with FG. However, revision of ARF definition as a parameter in calculating FGSI, UFGSI, SFGSI and ACCI may improve comparability of further studies.

REFERENCES

1. Baurienne H. Sur une plaie contuse qui's est terminee par le sphacele de le scrotum. J Med Chair Pharm 1764; 20:251-256.
2. Laor E, Palmer LS, Tolia BM, Reid RE, Winter HI. Outcome prediction in patients with Fournier's gangrene. J Urol 1995; 154(1):89-92.
3. Yilmazlar T, Ozturk E, Ozguc H, Ercan I, Vuruskan H, Oktay B. Fournier's gangrene: An analysis of 80 patients and a novel scoring system. Tech Coloproctol 2010; 14(3):217-223.
4. Roghmann F, von Bodman C, Loppenberg B, Hinkel A, Palisaar J, Noldus J. Is there a need for the Fournier's gangrene severity index? Comparison of scoring systems for outcome prediction in patients with Fournier's gangrene. BJU Int 2012; 110(9):1359-1365.
5. Lin TY, Ou CH, Tzai TS, Tong YC, Chang CC, Cheng HL, *et al*. Validation and simplification of Fournier's Gangrene Severity Index. Int J Urol 2014; 21(7):696-701.
6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987; 40(5):373-383.
7. Erdogan A, Aydogan I, Senol K, Uckan EM, Ersoz S, Tez M. Simple scoring system for prediction of mortality in Fournier's gangrene. Eur J Trauma Emerg Surg 2016; 42(4):513-518.
8. Erol B, Tuncel A, Tok A, Hanci V, Sari U, Sendogan F, *et al*. Low magnesium levels an important new prognostic parameter can be overlooked in patients with Fournier's gangrene: A multicentric study. Int Urol Nephrol 2015; 47(12):1939-1945.
9. Kahramanca S, Kaya O, Ozgehan G, Irem B, Dural I, Kucukpinar T, *et al*. Are neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as effective as Fournier's Gangrene Severity Index for predicting the number of debridements in Fourner's gangrene? Ulus Travma Acil Cerrahi Derg 2014; 20(2):107-112.
10. Bozkurt O, Sen V, Demir O, Esen A. Evaluation of the utility of different scoring systems (FGSI, LRINEC and NLR) in the management of Fournier's gangrene. Int Urol Nephrol 2015; 47(2):243-248.
11. Benjelloun el B, Souiki T, Yakla N, Ousadden A, Mazaz K, Louchi A, *et al*. Fournier's gangrene: Our experience with 50 patients and analysis of factors affecting mortality. World J Emerg Surg 2013; 8(1):13.
12. Tuncel A, Keten T, Aslan Y, Kayali M, Erkan A, Koseoglu E, *et al*. Comparison of different scoring systems for outcome prediction in patients with Fournier's gangrene: Experience with 50 patients. Scand J Urol 2014; 48(4):393-399.
13. Nisbet AA, Thompson IM. Impact of diabetes mellitus on the presentation and outcomes of Fournier's gangrene. Urology 2002; 60(5):775-779.
14. Sorensen MD, Krieger JN, Rivara FP, Klein MB, Wessells H. Fournier's gangrene: Management and mortality predictors in a population based study. J Urol 2009; 182(6):2742-2747.
15. Yanar H, Taviloglu K, Ertekin C, Guloglu R, Zorba U, Cabioglu N, *et al*. Fournier's gangrene: Risk factors and strategies for management. World J Surg 2006; 30(9):1750-1754.
16. Corcoran AT, Smaldone MC, Gibbons EP, Walsh TJ, Davies BJ. Validation of the Fournier's gangrene severity index in a large contemporary series. J Urol 2008; 180(3):944-948.
17. Erol B, Tuncel A, Hanci V, Tokgoz H, Yildiz A, Akduman B, *et al*. Fournier's gangrene: Overview of prognostic factors and definition of new prognostic parameter. Urology 2010; 75(5):1193-1198.
18. Yilmazlar T, Isik O, Ozturk E, Ozer A, Gulcu B, Ercan I. Fournier's gangrene: Review of 120 patients and predictors of mortality. Ulus Travma Acil Cerrahi Derg 2014; 20(5):333-337.
19. Jeong HJ, Park SC, Seo IY, Rim JS. Prognostic factors in Fournier gangrene. Int J Urol 2005; 12(12):1041-1044.
20. Korkut M, Içöz G, Dayangac M, Akgün E, Yeniay L, Erdoğan Ö, *et al*. Outcome analysis in patients with Fournier's gangrene. Dis Colon Rectum 2003; 46(5):649-652.
21. Kuo C, Wang WS, Lee CM, Liu CP, Tseng HK. Fournier's gangrene: Ten-year experience in a medical center in northern Taiwan. J Microbiol Immunol Infect 2007; 40(6):500-506.
22. Martinschek A, Evers B, Lampl L, Gerngross H, Schmidt R, Sparwasser C. Prognostic aspects, survival rate, and predisposing risk factors in patients with Fournier's gangrene and necrotizing soft tissue infections: Evaluation of clinical outcome of 55 patients. Urol Int 2012; 89(2):173-179.
23. Ronco C, Kellum JA, Mehta R. Acute dialysis quality initiative (ADQI). Nephrol Dial Transplant 2001; 16(8):1555-1558.
24. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Critical care 2013; 17(1):204.

Original Article

To study the response of locally advanced nasopharyngeal cancer to concurrent chemo-radiotherapy

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ABSTRACT

Objective: To ascertain the response of concurrent chemo-radiotherapy in patients with locally advanced (Stage III-IVB) nasopharyngeal carcinoma.
Design: It was a retrospective case series.
Setting: Institute of Nuclear Medicine and Oncology (INMOL), Lahore
Subjects: Thirty-three eligible patients out of 89 with stage III-IVB were included.
Interventions: The TNM staging used for this study was that described in the 7th edition of AJCC Cancer Staging Manual. Patients received two cycles of Cisplatin 75 mg/m^2 and 5-FU 1000 mg/m^2, D1 and D1-D5, thrice weekly as neo-adjuvant chemotherapy followed by definitive CCRT of 66-70 Gy in 33-35 fractions.
Main outcome measures: CT/MRI images were done after six weeks of completion of chemo-radiation and were compared with base line imaging for response evaluation. Three-year overall survival (OS), three-year local recurrence free survival (LRFS) and three-year distant metastatic free survival (DMFS) were primary endpoints of study.
Results: Median age of the patient population was 49 years. Male to female ratio was 1.75:1.00. WHO Type 1 keratinizing squamous cell carcinoma was the most common histology (48.5%), majority was presented in stage IVA (48.5%, n=16), T4 was common tumor size (66.7%, n=22) and N2 was the most common stage of nodal involvement (54.5%, n=18). Complete and partial responses were observed in 54.5% (n=18) and 27.3% (n=9) of the cases respectively. Three-year OS was 51.5% (n=17), LRFS was 81.8% and DMFS was 60.6%.
Conclusion: Chemo-radiotherapy is effective in locally advanced nasopharyngeal carcinoma in terms of complete response, partial response, OS, LRFS and DMFS.

KEY WORDS: complete response, locally advanced, nasopharyngeal cancer, overall survival

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is distinctive amongst head and neck cancers owing to its unique features regarding epidemiology, histological spectrum, clinical features, biological behavior and treatment response especially with chemotherapy and radiotherapy[1]. It is of rare occurrence and accounts for 0.7% of all malignancies. More or less 86,700 new cases of NPC were reported in 2012[2].

The nasopharynx lies immediately below the base of skull, so surgical resection with an acceptable margin is not achievable, especially in cases with more advanced local disease[3]. Early-stage disease has a generally successful control rate with radiotherapy, but local relapse and distant metastases are observed frequently in patients with locally and regionally advanced tumors if treated with radiotherapy alone[4,5].

Management of locally advanced disease with neo-adjuvant chemotherapy employing cisplatin-based regimen along with concurrent radiotherapy has shown treatment benefits. Cisplatin and 5-fluorouracil (5-FU) is the most commonly used regimen to attain good response[6,7]. The disease has a predilection for men and greater incidence is seen in younger ages, even in children below five years of age. Peak incidence is observed in the midst of 6th and 7th decades of life[8,9].

Rarity of the disease has resulted in scarceness of published literature with respect to disease characteristics and treatment outcomes. We are sharing here three years data of locally advanced NPC patients who were treated with concurrent chemo-radiotherapy in our hospital setting.

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The primary endpoint of the study is to evaluate the percentage of patients achieving three years local recurrence free survival (LRFS), distant metastasis free survival (3 y DMFS) and overall survival (3 y OS) in locally advanced nasopharyngeal carcinoma. The secondary end point is to assess pathological complete response and partial response (PR), assessed after six months of treatment completion in locally advanced nasopharyngeal carcinoma. Subset analysis with reference to age, histopathology, T-stage, N-stage, treatment interruptions and radiotherapy dose (66Gy vs. 70 Gy) was also performed.

SUBJECTS AND METHODS

This study was conducted at INMOL Cancer Hospital, Lahore. It is a tertiary care cancer hospital equipped with all kinds of diagnostic and therapeutic facilities, including outpatient, inpatient, chemotherapy ward and radiotherapy facilities including one linear accelerator, two Cobalt 60 machines as well as diagnostic radiology facilities like CXR, ultrasound, mammography, computed tomography scan, bone scan, positron-emission tomography-computer tomography, *etc*.

The study population included all cases of NPC registered at INMOL cancer hospital from 1st January 2012 to 30th December 2014. Non-probability purposive sampling was done.

Only patients with locally advanced non-metastatic (stage III-IVB) NPC were selected. This subgroup of patients was included following TNM staging in accordance with American Joint Committee on Cancer 7th edition published in 2010. The inclusion criterion of our study was pathologically proven NPC, III-IVB disease, 20-70 years age and either gender. The exclusion criteria were pregnancy, multiple co-morbidities, ECOG 3-4, history of previous malignancy or active double cancer and patients lost to follow up.

We have included all patients of NPC treated at INMOL cancer hospital fulfilling our selection criteria during period of our research, which were 33. The total number of patients that were enrolled in the hospital from 1st January 2012 to 30th December 2014 were 89. Seven patients out of 89 were metastatic, nine had histopathology other than carcinoma, and the remaining 40 patients did not fulfill the inclusion criteria. All included patients received two cycles of Cisplatin 75 mg/m^2 and 5-FU 1000 mg/m^2, D1 and D1-D5, thrice weekly as neo-adjuvant chemotherapy which was followed by definitive CCRT of 66-70 Gy in 33-35 fractions. Computed tomography / magnetic resonance imaging were done after six weeks of completion of chemo-radiation and were compared with base line imaging for response evaluation.

This was a retrospective case series. The medical record of these patients was searched from the patient files. Data regarding the pre-treatment and post-treatment variables of interest was entered in the data collection form. Patients were also contacted by telephone for the collection of data about their present health status. Later on, data was transferred to the SPSS (Statistical Software for Professional Studies) V. 20.00 for further analysis.

Variables of the study were age, sex, ECOG status, socio-economic status, histopathology, stage grouping, T-stage, N-stage, absorbed dose delivered, treatment interruptions (continuous vs. interrupted), response according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria, three-year OS, three-year LRFS and three-year DMFS. Response to treatment was assessed with the help of Response Evaluation Criteria in Solid Tumors 1.1 and divided response into four categories: complete response (CR) which meant all target lesions disappeared on post-treatment imaging; partial response (PR) characterized as a 30% reduction in size or more of the target lesions; stable disease signifying any change in size ranging from a reduction of under 30% to an increase below 20% in the sum of the long axes of target lesions; and finally progressive disease amounting to an increase in size of 20% or more in the sum of long axes of target lesions. The same imaging modality was used for response assessment as was used for the patient at the time of staging workup (Computed tomography / magnetic resonance imaging) to ensure consistency of measurement. All patients were assessed radiologically six weeks after completion of treatment. Since NPC is known to regress up to 12 weeks after completion of treatment, those patients that were evaluated to be showing were radiologically evaluated a second time at three months post-treatment. In equivocal cases where radiologist could not distinguish PR or stable disease from radiation induced fibrotic changes, endoscopic biopsy was carried out to confirm response to treatment.

Patient data was recorded in the patient's performa and transferred to SPSS software, for data entry and analysis. The data collected was analyzed for all the above-mentioned variables. Frequency distribution tables were generated for certain variables like age, sex, socioeconomic class, histopathology, over all stage, *etc*. Later on, data was further analyzed to check the impact of different variables on CR, PR, three-year OS, LRFS or DMFS. The study adhered to CONSORT guidelines and approved by institutional review board. The study followed the principles of the contemporary revision of the Declaration of Helsinki.

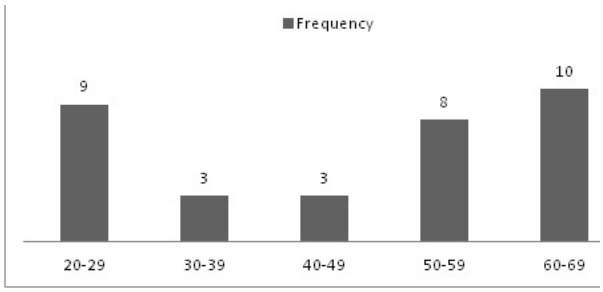

Fig 1: Age distribution of patients (years)

RESULTS

Patient characteristics

Median age of the patient population was 49 years (range: 20-69 years). Age distribution of the patients demonstrated that 30.3% (n=10) of patients were between 60-69 years, 24.2% (n=8) were between 50-59 years and 27.3% (n= 9) aged between 20-29 years (Fig 1). Male to female ratio was 1.75:1.00 and 66.7% (n=22) had ECOG-2 performance status. Keratinizing squamous cell carcinoma (SCC, WHO Grade 1) was the commonly observed histology 48.5% (n=16) followed by non-keratinizing undifferentiated SCC which was observed in 24.2% (n= 8) patients. Basaloid carcinoma was seen in 15.1% (n=5) of patients (Table 1). The majority of the patient population presented in stage IVA (48.5%, n=16), the commonly observed tumor size was T4 (66.7%, n=22) and commonly occurring nodal involvement was N2 (54.5%, n=18) (Table 1). Distribution of the patients by occupation demonstrated that 30.3% (n=10) of patients were house wives, 21.2% (n=7) were laborers, 18.2% (n=6) were students, 15.1% (n=5) were farmers, 6.1% (n=2) were drivers, and teacher, private cook and lawyer were one each making 3.03% in each category, (Fig 2).

Table 1: Patient characteristics

Characteristics	Frequency	Percentage
Gender distribution		
Male	21	63.6
Female	12	36.4
ECOG performance status		
ECOG-1	11	33.3
ECOG-2	22	66.7
Histopathology		
Keratinizing SCC	16	48.5
Non-keratinizing well-differentiated SCC	3	9.09
Non-keratinizing un differentiated SCC	8	24.2
Basaloid carcinoma	5	15
Adenoid cystic carcinoma	1	3.03
Stage distribution		
Stage III	9	27.27
Stage IVA	16	48.48
Stage IVB	8	24.24
T-stage distribution		
T1	1	3.03
T2	3	9.09
T3	7	21.21
T4	22	66.67
N-stage distribution		
N0	3	9.09
N1	4	12.12
N2	18	54.55
N3a	6	18.18
N3b	2	6.06

SCC: squamous cell carcinoma

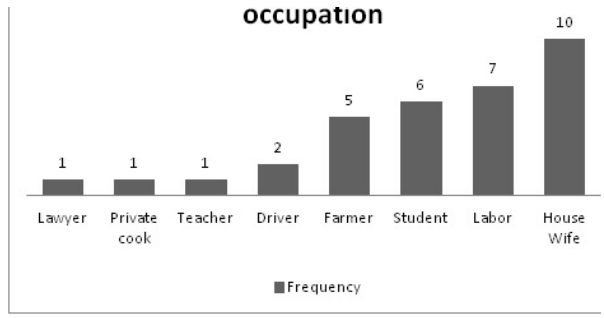

Fig 2: Distribution of patients by occupation

Response to treatment

Out of 33 patients, 54.5% (n=18) achieved CR, 27.3% (n=9) showed PR and 18.2% (n=6) patients showed progression on treatment (Table 2). Gender wise treatment response was 57.1% vs. 50.0% in male and female patients respectively showing no significant

Table 2: Treatment response in study population

Factor	CR (n/%)	PR (n/%)	PD (n/%)
Gender			
Male (n=21)	12 (57.1)	6 (28.6)	3 (14.3)
Female (n=12)	6 (50.0)	3 (25.0)	3 (25.0)
P-value	.692	.825	.443
Histopathology			
Keratinizing SCC (n=16)	11 (68.8)	2 (12.5)	3 (18.8)
Non keratinizing well-differentiated SCC (n=3)	2 (66.7)	1 (33.3)	0 (.0)
Non keratinizing undifferentiated SCC (n=8)	2 (25.0)	5 (65.5)	1 (12.5)
Adenoid cystic carcinoma (n=1)	1 (100.0)	0 (.0)	0 (.0)
Basaloid (n=5)	2 (40.0)	1 (20.0)	2 (40.0)
P-value	.235	.119	.615
Stage wise treatment response			
III (n=9)	7 (77.8)	1 (11.1)	1 (11.1)
IVA (n=16)	8 (50.0)	5 (31.2)	3 (18.8)
IVB (n=8)	3 (37.5)	3 (37.5)	2 (25.0)
P-value	.220	.420	.757
Treatment interruption			
Continuous (n=26)	16 (61.5)	6 (23.1)	4 (15.4)
Interrupted (n=7)	2 (28.6)	3 (42.9)	2 (28.6)
P-value	.120	.297	.422
Radiation dose			
66 Gy (n=5)	2 (40.0)	3 (60.0)	0 (.0)
70 Gy (n=28)	16 (57.1)	6 (21.4)	6 (21.4)
P-value	.478	.074	.252
Overall	18 (54.5)	9 (27.3)	6 (18.2)

CR: complete response; PR: partial response; PD: progressive disease; SCC: squamous cell carcinoma

difference (*P*=.692). CR was 68.8% in keratinizing SCC, 66.7% in non-keratinizing well-differentiated SCC, 40% in basaloid and 25% in non-keratinizing undifferentiated SCC. One patient had adenoid cystic carcinoma that had shown CR to treatment (Table 2). Overall, no significant difference was observed in treatment response with varying histopathologies (*P*=.235), (Table 2).

Maximum CR was observed in patients enrolled in stage III (77.8%) which decreased gradually as the stage was increased *i.e.*, 50% in IVA and 37.5% in IVB but showing no statistically significant difference (*P*=.220). Patients receiving continuous treatment had 61.5% CR, which was higher than the patients with interrupted treatment (28.6%), *P*-value was not significant again (Table 2). Patients receiving 70 Gy vs. 66 Gy had 57.1% vs. 40% CR with *P*=.478 (Table 2).

Three-year OS was achieved by 51.5% (n=17) patients (Table 3). Local recurrence was observed in 18.2% (n=6) and distant metastases was seen in 39.4% (n=13) over a 3-year follow-up period (Table 3). Hence, three-year OS was 51.5%, three-year LRFS remained 81.8% and three-year DMFS was 60.6% in overall patient population.

Local recurrence was 14.3% in males and 25% in female patients while, distant metastasis was 33.3% and 50% in male and female patients, respectively. Three-year OS was also better in males as compared to female patients, being 61.9% and 33.3% in male and female patients respectively. Although male patients had shown comparatively superior disease control and OS but difference was not statistically significant (Table 3).

Similarly, treatment interruptions or radiation dose (66 Gy vs. 70 Gy) did not show statistically significant affect on the local recurrence, distant metastasis and three-year OS in our study sample. Histopathology had significant effect (*P*=.024) on three-year OS. Patients with non-keratinizing well differentiated SCC and adenoid cystic carcinoma had 100% three-year OS, while in basaloid carcinoma prognosis was poor and no patient out of five was able to achieve three-year OS. Local recurrence (*P*=.253) and distant metastasis (*P*=.301) were however not significantly different with respect to histopathologies (Table 3).

Disease stage had significant effect on distant metastasis (*P*<.001) and patients with stage IVB at presentation developed 100% (8 out of 8 patients) distant metastasis while the rate was 0% (0 out of 9) in stage III. In the patients presented at stage IVA distant metastasis was 31.2% (5 out of 16) patients (Table 3). Variables of study including gender, histopathology, stage, treatment interruption and radiation dose had no significant effect on treatment outcome in terms of CR, PR and progressive disease (Table 2).

Table 3: Relapse status and overall survival

Parameters	Local Recurrence (n=6)	Distant Metastasis (n=13)	Overall 3-year Survival (n=17)
Gender			
Male (n=21)	3 (14.3)	7 (33.3)	13 (61.9)
Female (n=12)	3 (25.0)	6 (50.0)	4 (33.3)
P-value	.443	.346	.114
Histopathology			
Keratinizing SCC (n=16)	3 (18.8)	6 (37.5)	7 (43.8)
Non keratinizing well differentiated SCC (n=3)	0 (.0)	1 (33.3)	3 (100.0)
Non keratinizing undifferentiated SCC (n=8)	1 (12.5)	2 (25.0)	6 (75.0)
Adenoid cystic carcinoma (n=1)	1 (100.0)	0 (.0)	1 (100.0)
Basaloid (n=5)	1 (20.0)	4 (80.0)	0 (.0)
P-value	.253	.301	.024
Stage wise treatment response			
III (n=9)	1 (11.1)	0 (.0)	7 (77.8)
IVA (n=16)	5 (31.2)	5 (31.2)	6 (37.5)
IVB (n=8)	0 (.0)	8 (100.0)	4 (50.0)
P-value	.141	<.001	.153
Treatment interruptions			
Continuous (n=26)	6 (23.1)	10 (38.5)	15 (57.5)
Interrupted (n=7)	0 (.0)	3 (42.9)	2 (28.6)
P-value	.160	.833	.171
Radiation dose			
66 Gy (n=5)	2 (40.0)	2 (40.0)	3 (60.0)
70 Gy (n=28)	4 (14.3)	11 (39.3)	14 (50.0)
P-value	.170	.976	.680
Overall (n=33)	6 (18.2)	13 (39.4)	17 (51.5)

SCC: squamous cell carcinoma

DISCUSSION

The present study was a retrospective single arm observational study, which was conducted to evaluate the efficacy of concurrent chemoradiotherapy (CCRT) for locally advanced stage (III-IVB) nasopharyngeal carcinoma patients from central Punjab, Pakistan. The efficacy was evaluated in terms of three-year OS as well as local and distant recurrences over a three-year follow-up period. An attempt was made to observe the effects of limitations common in third world countries such as gender discrimination, under-dosing *i.e.* prescribed doses less than 70 Gy due to conventional treatment planning and frequent treatment interruptions due to machine down-time.

Nasopharyngeal carcinoma is sensitive to both radio and chemotherapy. Stage I disease is treated with radiotherapy alone but for locoregionally advanced NPC, CCRT with or without adjuvant chemotherapy is the standard of care[10-13].

Dose recommendation for gross tumor control is 70 Gy whereas either 50-60 Gy or 46-60 Gy may be chosen for the potential risk sites involved. For radiotherapy delivery, two dimensional (2D) radiotherapy is the minimum prerequisite and that too if there is no intracranial extension of disease, while three dimensional (3D) and IMRT are the modes of choice wherever available[14-16].

Intergroup 0099 study was the first randomized trial to show a survival benefit with chemoradiotherapy. A 31% increase in three-year OS was reported in the group where 5FU/Cisplatin based chemotherapy was added along with radiotherapy[7].

In our study, all patients received two cycles of 5FU/Cisplatin as neoadjuvant therapy followed by definitive CCRT. In overall patient population, three-year OS was 51.5%, three-year LRFS remained 81.8%, three-year DMFS was 60.6% and CR was 54.5%.

A recent phase III multicentre randomised controlled trial has shown three-year OS of 88.2%, three-year DMFS of 86% and three-year LRFS of 94.3% with neoadjuvant chemotherapy followed by CCRT. Complete response was 41.6% in their trial[13].

CR in our study was comparable to the literature; however, our results differed from the results of previous studies in terms of OS, local recurrence, and distant metastasis[17,18]. The possible explanations for these differences includes small sample size (n=33), about half of the patients having unfavourable histology, about a third of the patients with advanced age (60-69 years) and low socio-economic status possibly translating into delayed treatment seeking by the patient. Furthermore, because of low socio-economic status, patients may not be able to complete recommended metastatic workup leading to patients being understaged.

In our study, histopathology had a significant effect on three-year OS with keratinized squamous and basaloid varieties faring poorly in comparison to others (P=.024; Table 3) although histopathology did not seem to impact significantly on response at end of treatment (Table 2).

Disease stage has been shown to significantly affect the treatment outcomes in locally advanced NPC[19]. Disease stage affected incidence of developing distant metastases and reducing DMFS significantly in our study (P<.001; Table 3). Decline in probability of CR, local control and three-year OS is also seen in our study but the difference is not statistically significant with the current patient number in our study.

Patient gender did not seem to have a statistically significant effect on response to treatment in our population (Table 2). Furthermore, incidence of local recurrence and distant metastasis as well as the three-year OS was statistically the same in both sexes (P=.443, .346 & .114 respectively; Table 3)

With regards to total dose received, our patients comprised of two groups: one having been planned conventionally received 66 Gy while the second group comprised of conformal planned patients who received 70 Gy. No statistically significant difference was captured in treatment response, local recurrence incidence, distant metastasis or three-year OS in the two groups (Tables 2 and 3). However, the increase in number of partial responders in the 70 Gy subset does seem to be approaching significance (P=.074; Table 2) and thus further investigation with a larger number of patients is warranted.

Treatment interruptions are reported to influence local control rates in previous studies[20]. However, treatment interruptions due to machine down-time did not yield any statistically significant difference in treatment response, local recurrence incidence, distant metastasis incidence and three-year OS (Table 2 and 3). It may be because none of the patients met with a treatment interruption extending beyond three days and a compensatory dose of 0.6 Gy/day was added to the total prescribed dose for every interrupted day. Another reason of no significant difference of treatment interruptions in our study may be very small number of patients (n=7) having interrupted treatment.

CONCLUSION

In conclusion, addition of neoadjuvant chemotherapy followed by Chemo-radiotherapy seems to be an effective strategy in treating locally advanced nasopharyngeal carcinoma in terms of treatment response, three-year overall survival, local recurrence free survival and distant metastasis free survival. Stage and histopathology seem to have significant effect on treatment response and patient survival. A study

comprising of a larger sample size is needed to further investigate effects of total prescribed dose (66Gy vs. 70 Gy) as well as routine treatment interruptions.

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REFERENCES

1. Fuwa N, Kodaira T, Daimon T, Yoshizaki T. The long-term outcomes of alternating chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a multiinstitutional phase II study. Cancer Med 2015; 4(8):1186-1195.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65(2):87-108.
3. Liu ZG, Zhao Y, Tang J, Zhao YJ, Yang WJ, Qiu YF, *et al*. Nimotuzumab combined with concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: a retrospective analysis. Oncotarget 2016; 7(17): 24429-24435.
4. Yoshizaki T, Ito M, Murono S, Wakisaka N, Kondo S, Endo K. Current understanding and management of nasopharyngeal carcinoma. Auris Nasus Larynx 2012; 39(2):137-144.
5. Lee AWM, Ng WT, Chan YH, Sze H, Chan C, Lam TH. The battle against nasopharyngeal cancer. Radiother Oncol 2012; 104(3):272-278.
6. Decker DA, Drelichman A, Al-Sarraf M, Crissman J, Reed ML. Chemotherapy for nasopharyngeal carcinoma. A ten-year experience. Cancer 1983; 52(4):602-605.
7. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, *et al*. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998; 16(4):1310-1317.
8. Safavi-Naini A, Raad N, Ghorbani J, Chaibakhsh S, Ramezani-Daryasar R. Incidence trends and geographical distribution of nasopharyngeal carcinoma in Iran. Iran J Cancer Prev 2015; 8(1):24-28.
9. Tan WL, Tan EH, Lim DWT, Ng QS, Tan DSW, Jain A, *et al*. Advances in systemic treatment for nasopharyngeal carcinoma. Chin Clin Oncol 2016; 5(2):21.
10. Mahdavifar N, Ghoncheh M, Hafshejani AM, Khosravi B, Salehiniya H. Epidemiology and inequality in the incidence and mortality of nasopharynx cancer in Asia. Osong Public Health Res Perspect 2016; 7(6):360-372.
11. Xie SH, Yu ITS, Tse LA, Mang OW, Yue L. Sex difference in the incidence of nasopharyngeal carcinoma in Hong Kong 1983-2008: suggestion of a potential protective role of oestrogen. Eur J Cancer 2013; 49(1):150-155.
12. Xiao G, Cao Y, Qiu X, Wang W, Wang Y. Influence of gender and age on the survival of patients with nasopharyngeal carcinoma. BMC Cancer 2013; 13:226.
13. Cao SM, Yang Q, Guo L, Mai HQ, Mo HY, Cao KJ, *et al*. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: A phase III multicentre randomised controlled trial. Eur J Cancer 2017; 75:14-23.
14. Lee AWM, Lau WH, Tung SY, Chua DTT, Chappel R, Xu L, *et al*. Hong Kong Nasopharyngeal Cancer Study Group. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol 2005; 23(28):6966-6975.
15. Nasopharyngeal Carcinoma Union for International Cancer Control 2014 Review of Cancer Medicines on the WHO List of Essential Medicines. 2014; 1-9.
16. Hu QY1, Liu P, Wang L, Fu ZF. Concurrent chemoradiotherapy followed by adjuvant chemotherapy for stage III-IVa nasopharyngeal carcinoma. Ai Zheng 2007; 26(4):394-397.
17. Wang Y, Ding W, Chen C, Niu Z, Pan M, Zhang H. Meta-analysis of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma. J Cancer Res Ther 2015; 11(6):191-195.
18. Zhang L, Zhao C, Ghimire B, Hong MH, Liu Q, Zhang Y, *et al*. The role of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of the phase III randomized trials. BMC Cancer 2010; 15(10):558.
19. Wang F, Jiang C, Ye Z, Liu T, Sun Q, Yan F, *et al*. Treatment outcomes of 257 patients with locoregionally advanced nasopharyngeal carcinoma treated with nimotuzumab plus intensity-modulated radiotherapy with or without chemotherapy: A single-institution experience. Transl Oncol 2018; 11(1):65-73.
20. Ekici K, Aksu A, Temelli O, Mayadagli A, Ceylaner B, Ozseker N, *et al*. Retrospective investigation of 49 cases of locally advanced nasopharyngeal cancer patients who were given neoadjuvant docetaxel/cisplatin chemotherapy and concomitant chemoradiotherapy. UHOD 2014; 24(3):171-178.

Case Report

Transient liver involvement with non-disseminated cutaneous zoster: A case report and review of the literature

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ABSTRACT

Herpes zoster (HZ) occurs due to the reactivation of latent varicella zoster virus in the cranial or spinal sensory nerve ganglia. This results in the development of grouped skin vesicles in a classic unilateral dermatomal distribution. Visceral involvement in HZ is uncommon and is mainly reported in cases with cutaneous dissemination. We report an unusual case of non-disseminated HZ associated with transient elevation of liver enzymes. We also discuss possible mechanisms responsible for the associated liver involvement and review the literature on visceral HZ.

KEY WORDS: liver enzymes, transient, visceral, zoster

INTRODUCTION

Herpes zoster (HZ) is a common skin condition that results from reactivation of varicella zoster virus (VZV). Primary VZV infection usually presents during childhood with a generalized vesicular eruption classically known as chickenpox. The virus then remains dormant in spinal or cranial sensory ganglia and might get reactivated later in life[1]. When VZV gets reactivated, painful grouped vesicles develop on one side of the body in a dermatomal distribution. Appearance of skin lesions is typically preceded by prodromal pain along the same dermatome for a few days[1,2]. The rash spontaneously resolves within one to two weeks[2]. Risk factors leading to a reduction in the cellular immune response, and subsequently HZ, include immunosuppression and advancing age[3].

Several complications have been associated with HZ. Post-herpetic neuralgia is the most common complication occurring in approximately 15% of patients[3]. Other less common sequelae include ocular complications (such as retinopathy), neurological disease (such as meningoencephalitis and stroke), and visceral involvement[3,4]. Visceral involvement is rare and usually occurs in patients with disseminated cutaneous HZ[5]. In disseminated cutaneous HZ, multiple scattered vesicles develop far from the primarily affected dermatome[1]. We report a case of visceral involvement in the form of transient elevation of liver enzymes. The patient had classic dermatomal non-disseminated HZ. We also review the literature with regards to visceral HZ.

CASE REPORT

A 52-year-old female presented to the emergency department with a skin rash over the right side of the back for two days. Five days prior to the rash, there was stabbing pain radiating from the back to right chest. She was recently diagnosed with pemphigus vulgaris and has been on azathioprine 100 mg daily plus a tapering dose of prednisolone over the past six months. The patient was not started on any other medications recently and denied taking any herbal

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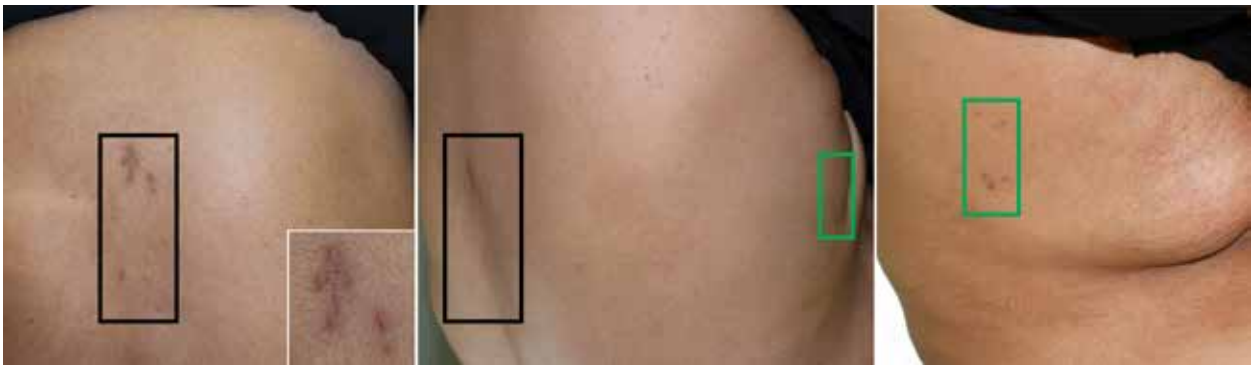

Fig 1: Herpes zoster. Grouped crusted erosions involving the right side of the back (black rectangles) and right lateral chest wall (green rectangles) along the T5 to T7 dermatomes. A close-up view of the grouped erosions is shown (inset).

medicine. The patient was otherwise well, with no fever or any other systemic symptoms. Skin examination revealed several grouped vesicles on an erythematous base involving the right side of the back and right lateral chest wall along the dermatomes T5 to T7 (Fig 1). Full skin examination did not show any vesicles affecting other parts of the body. Direct fluorescent antibody assay and viral culture of samples taken from skin vesicles were positive for VZV. The patient was treated for non-disseminated HZ with famciclovir 500 mg orally every eight hours for seven days.

The onset of zoster pain coincided with the day of routine blood investigations to monitor azathioprine side effects. Alanine transaminase (ALT) and aspartate transaminase (AST) were both elevated (ALT: 71 U/L (normal: 5-55 U/L); AST: 36 U/L (normal: 5-34 U/L), Fig 2). A full liver function test was requested (two weeks after the onset of zoster pain). It showed elevated gamma-glutamyl transpeptidase (GTP: 1459 U/L; normal: 9-36 U/L) and alkaline phosphatase (ALP: 310 U/L; normal: 40-150 U/L); however, ALT and AST normalized (Fig 2, Fig 3). Azathioprine was not put on hold due to normalization of ALT and AST. Total protein, bilirubin levels, renal function and lipid profile were within normal limits. Anti-hepatitis B core and anti-hepatitis B surface antibodies were positive; however, hepatitis B surface antigen was negative indicating immunity due to previous hepatitis B virus infection. Furthermore, hepatitis B virus DNA was undetected in the blood. Hepatitis C serology, antinuclear antibody and anti-smooth muscle antibodies were all negative. Liver ultrasound showed changes suggestive of fatty liver.

Over the following two months, serial liver function tests showed a gradual reduction in the levels of GTP and ALP, along with the improvement of the zoster pain and rash. ALP returned to normal levels; however, GTP remained slightly elevated (215 U/L). Based on the overall clinical and laboratory findings, the transient elevation in liver enzymes was attributed to HZ. The

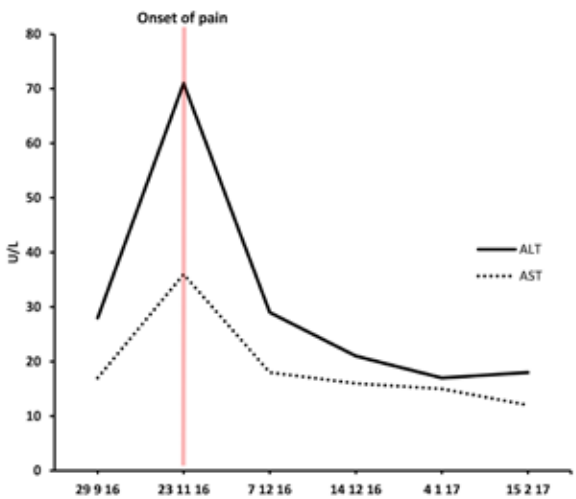

Fig 2: Elevation of alanine transaminase (ALT) and aspartate transaminase (AST) around the onset of zoster pain. Both normalized within two weeks.

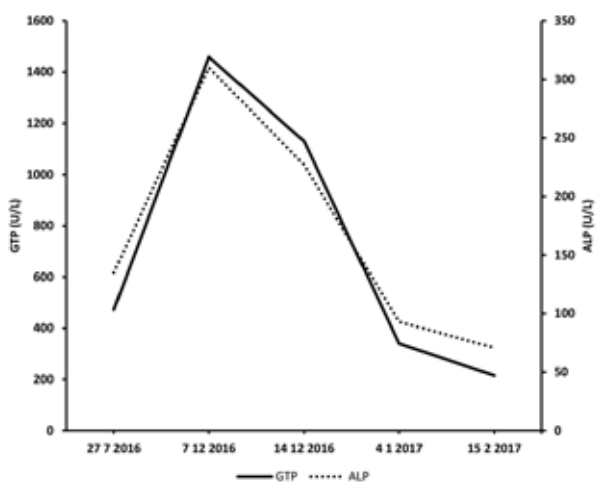

Fig 3: Elevated gamma-glutamyl transpeptidase (GTP) and alkaline phosphatase (ALP). Levels significantly decreased within one month.

persistent mild GTP elevation was thought to be due to the fatty liver changes found on ultrasound.

DISCUSSION

Apart from the classic localized dermatomal pattern, HZ has other less common presentations. Those include dermatomal HZ with cutaneous dissemination, atypical generalized (non-dermatomal) vesicles, and visceral zoster in the absence of cutaneous lesions[5,6]. Cutaneous dissemination in dermatomal HZ is considered when there are more than 20 vesicles outside the primary dermatomes involved[5].

Visceral HZ is rare. In a study of 450 renal transplant patients, none of those who developed cutaneous HZ had visceral involvement[7]. Visceral HZ developed in less than 1% (20 cases) of 2411 patients who underwent hematopoietic stem cell transplantation[8]. Visceral involvement occurs more in patients with widespread skin involvement and less likely in those with localized dermatomal non-disseminated HZ[5,8].

The diagnosis of visceral HZ is based on positive tissue culture for VZV, histologic evidence of VZV, or clinical findings suggestive of internal organ involvement in the presence of cutaneous HZ after exclusion of other causes[8,9]. Variable degrees of liver involvement have been reported in up to 25% of children with primary VZV infection[10]. However, reports indicating liver abnormalities are uncommon in patients with HZ. Most cases were reported in patients with disseminated dermatomal HZ[5], atypical generalized non-dermatomal HZ[11], or those without skin lesions[12].

Our patient had localized dermatomal non-disseminated HZ that was associated with transient liver enzyme elevation, but was clinically well otherwise. Suarez Santisteban MA *et al*[13] reported a similar presentation in a patient with ANCA vasculitis on prednisone and mycophenolate mofetil. The patient presented with abdominal pain and dyspnea, in addition to zoster affecting the dermatomes T9 to T11. He was found to have severe liver abnormalities and bilateral lung infiltrates. Both the liver and lung abnormalities normalized after treatment with acyclovir. In a study of VZV infections in 109 pediatric cases post hematopoietic stem cell transplantation, 25% developed HZ[14]. Only one child with localized dermatomal non-disseminated HZ was reported to have ALT elevation[14].

In another study of 310 children post hematopoietic stem cell transplantation, ALT levels prior to the development of HZ were analyzed[9]. Seventy-six (25%) of them developed HZ and at least 29% (n=22) of those with HZ were found to have elevated ALT prior to the development of skin rash. However, it was not clear from the study whether the cases associated with ALT elevation had localized or disseminated HZ. Moreover, the exact location of the dermatomes affected in those with elevated ALT was not specified.

Involvement of both the skin and liver has been attributed to either centripetal spread of the virus toward the viscera as a sequence of sharing the same dorsal root ganglion or hematogenous spread[5]. In our case, the affected dermatomes were T5 to T7. The sympathetic component of the hepatic plexus arises from the T7 to T12 segments of the spinal cord[15,16]. Hence, VZV reactivation in our patient likely resulted in its spread through the dorsal ganglion to both the skin and liver. Transient VZV viremia might have occurred and resulted in hematogenous spread of the virus to the liver. Nevertheless, this is a remote possibility in our patient since she did not have cutaneous dissemination, which is more likely to be associated with VZV viremia. However, this possibility cannot be excluded as testing for VZV viremia was not performed.

CONCLUSION

We report a patient with localized dermatomal non-disseminated HZ associated with transient liver enzyme elevation that was coincidentally found on routine blood testing. This phenomenon appears to be under-reported since patients are probably clinically asymptomatic. We hypothesize that this transient abnormality occurred due to neural spread of VZV to both the skin and liver. Therefore, HZ should be included in the differential diagnosis of abnormal liver enzymes. Further studies with more details of cutaneous characteristics of HZ are required in order to better characterize this interesting phenomenon.

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REFERENCES

1. Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG, *et al*. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv Vaccines 2015; 3(4):109-120.
2. Gilden D, Nagel MA, Cohrs RJ. Varicella-zoster. Handb Clin Neurol 2014; 123:265-283.
3. Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, Gilden D, *et al*. Varicella zoster virus infection. Nat Rev Dis Primers 2015; 1:15016.
4. Galetta KM, Gilden D. Zeroing in on zoster: A tale of many disorders produced by one virus. J Neurol Sci 2015; 358(1-2):38-45.
5. Stratman E. Visceral zoster as the presenting feature of disseminated herpes zoster. J Am Acad Dermatol 2002; 46(5):771-774.

6. Vora RV, Anjaneyan G, Kota RKS, Pilani AP, Diwan NG, Patel NN. Study of clinical profile of herpes zoster in human immunodeficiency virus positive and negative patients at a rural-based tertiary care center, Gujarat. Indian J Sex Transm Dis AIDS 2017; 38(1):65-68.
7. Pavlopoulou ID, Poulopoulou S, Melexopoulou C, Papazaharia I, Zavos G, Boletis IN. Incidence and risk factors of herpes zoster among adult renal transplant recipients receiving universal antiviral prophylaxis. BMC Infect Dis 2015; 15:285.
8. Doki N, Miyawaki S, Tanaka M, Kudo D, Wake A, Oshima K, *et al*. Visceral varicella zoster virus infection after allogeneic stem cell transplantation. Transpl Infect Dis 2013; 15(3):314-318.
9. Berman JN, Wang M, Berry W, Neuberg DS, Guinan EC. Herpes zoster infection in the post-hematopoietic stem cell transplant pediatric population may be preceded by transaminitis: An institutional experience. Bone Marrow Transplant 2006; 37(1):73-80.
10. Gallegos-Orozco JF, Rakela-Brodner J. Hepatitis viruses: not always what it seems to be. Rev Med Chil 2010; 138(10):1302-1311.
11. Milligan KL, Jain AK, Garrett JS, Knutsen AP. Gastric ulcers due to varicella-zoster reactivation. Pediatrics 2012; 130(5):e1377-1381.
12. Saitoh H, Takahashi N, Nanjo H, Kawabata Y, Hirokawa M, Sawada K. Varicella-zoster virus-associated fulminant hepatitis following allogeneic hematopoietic stem cell transplantation for multiple myeloma. Intern Med 2013; 52(15):1727-1730.
13. Suarez Santisteban MA, Garcia-Bernalt Funes MV, Mora Mora M, Novillo Santano RA, Rangel Hidalgo G, Cebrian C. Varicella zoster virus: Complications in an ANCA-positive vasculitis. Nefrologia 2011; 31(5):616-618.
14. Leung TF, Chik KW, Li CK, Lai H, Shing MM, Chan PK, *et al*. Incidence, risk factors and outcome of varicella-zoster virus infection in children after haematopoietic stem cell transplantation. Bone Marrow Transplant 2000; 25(2):167-172.
15. Jensen KJ, Alpini G, Glaser S. Hepatic nervous system and neurobiology of the liver. Compr Physiol 2013; 3(2):655-665.
16. Mizuno K, Ueno Y. Autonomic nervous system and the liver. Hepatol Res 2017; 47(2):160-165.

Case Report

Rupture of pyometra and septic shock after LeFort colpocleisis: A case report

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ABSTRACT

An 80-year-old gravida 3 para 2 woman who had been in menopause for 30 years presented to our clinic with symptoms of total uterine prolapse and stress urinary incontinence. LeFort colpocleisis and transobturator tape surgery was performed due to the patient's age. Seven months postoperatively, the patient presented to the emergency department with symptoms of abdominal pain. The abdominal examination revealed a distended abdomen that was severely tender to palpation, with rigidity, guarding and rebound tenderness. Trans-abdominal ultrasonography evaluation showed the presence of intra-abdominal fluid collection and free air. Abdominal computed tomography confirmed the intra-abdominal generalized fluid collection, and a 10 cm mass consistent with an abscess neighboring the bladder was detected. The patient underwent laparotomy with the diagnosis of acute abdomen, and approximately 1500-2000 cc purulent material was drained. The surgical exploration revealed no gastrointestinal perforation. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed with the diagnosis of spontaneous rupture of pyometrium. The patient died of septic shock and multiple organ failure on postoperative day 15 in the intensive care unit. Patients presenting with spontaneous pyometrium rupture must be treated through drainage, antibiotherapy and hysterectomy, if required, due to high rates of mortality and morbidity associated with this condition.

KEY WORDS: LeFort operation, pyometra, septic shock

INTRODUCTION

Pyometrium is the accumulation of purulent material in the uterine cavity due to dysfunctional drainage of physiologic secretions as a consequence of cervical stenosis[1-3]. Its frequency is 0.1-0.5% in the gynecologic patient population; however, this frequency may reach 13.6% in postmenopausal patients[1,3,4].

Causes of cervical stenosis include gynecologic malignancies such as cervical cancer; benign pathologies such as endometrial polyps, myoma uteri and senile cervicitis; retained intrauterine devices, radiotherapy and postoperative cervical adhesions following gynecological surgeries[1-3,5].

Although some patients with ruptured pyometrium may present to the emergency room with the clinical triad of abdominal pain, purulent discharge and postmenopausal bleeding, more than 50% of such patients are asymptomatic[2]. Pneumoperitoneum, defined as the presence of intra-abdominal free air, which often occurs after bowel perforation is also detected in pyometrium rupture[6].

CASE REPORT

An 80-year-old G3 P2 woman who had been in menopause for 30 years presented to our clinic with symptoms of total uterine prolapse and stress urinary incontinence. LeFort colpocleisis and transobturator

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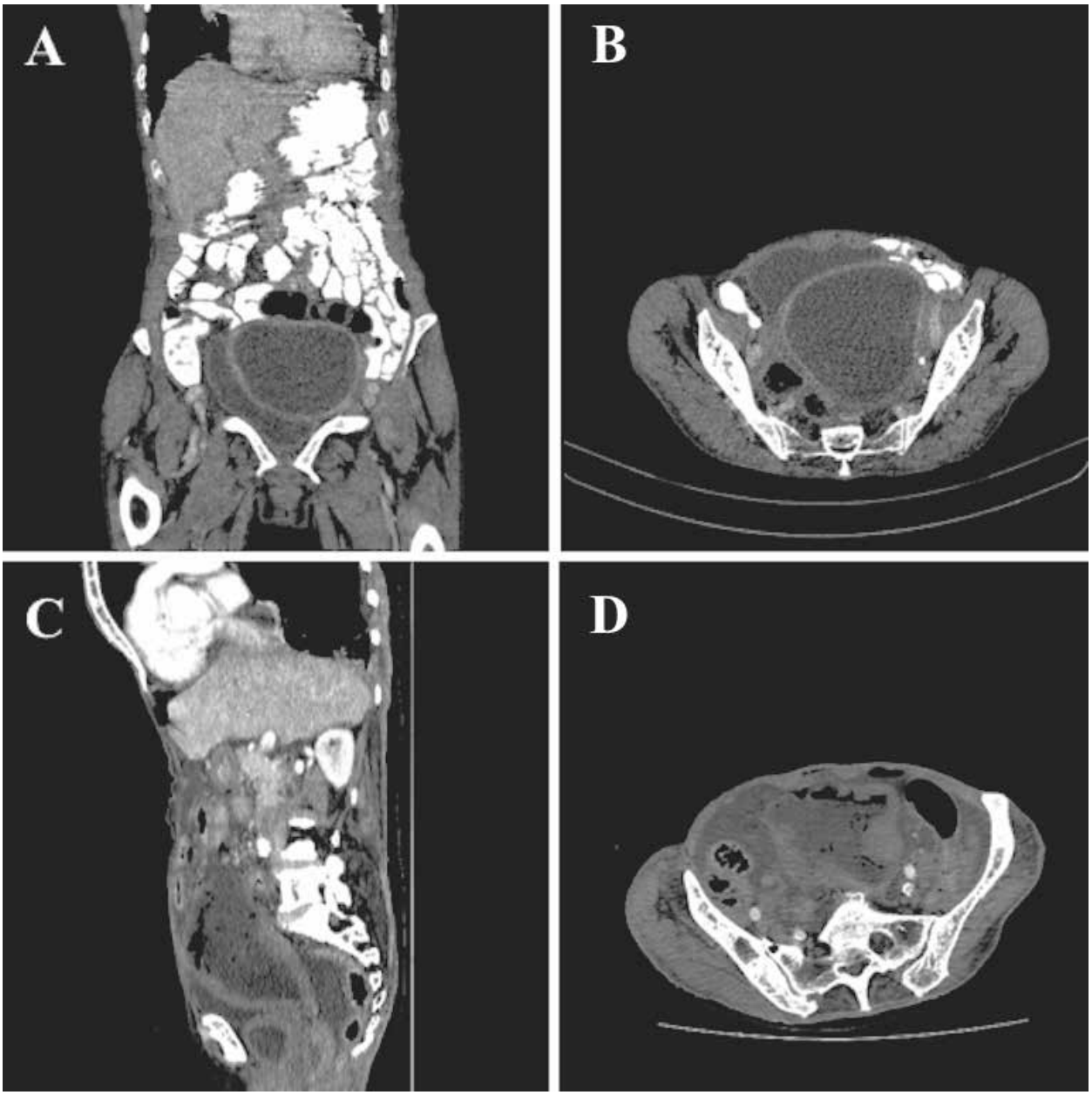

Fig 1: A-B, view of the abdominal CT scan before uterine rupture on the 4th postoperative month (LeFort colpocleisis); **C-D**, abdominal CT scan revealed the intra-abdominal fluid collection and free air on the 7th postoperative month (LeFort colpocleisis)

midurethral sling was performed due to the patient's advanced age and presence of hypertension. Although the patient experienced no problems in the early postoperative period, she presented to the gynecology clinic four months postoperatively with abdominal pain and minimal purulent vaginal discharge. Abdominal computed tomography (CT) revealed fluid in the uterus (Figure 1). Drainage and antibiotherapy were recommended; however, the patient refused the recommended treatment.

The patient was admitted to the emergency department again on the 7th postoperative month with symptoms of abdominal pain. Her vital signs were: blood pressure 90/60 mmHg; heart rate 72 beats/minute; body temperature 36.8 °C. During the physical examination, the patient was diaphoretic, uncomfortable and in severe distress. The abdominal examination revealed a distended abdomen that was severely tender to palpation, with rigidity, guarding and rebound tenderness. Decreased bowel sounds were heard. Trans-abdominal ultrasonography evaluation showed the presence of intra-abdominal fluid collection and free air. Abdominal CT confirmed the intra-abdominal fluid collection and free air, and

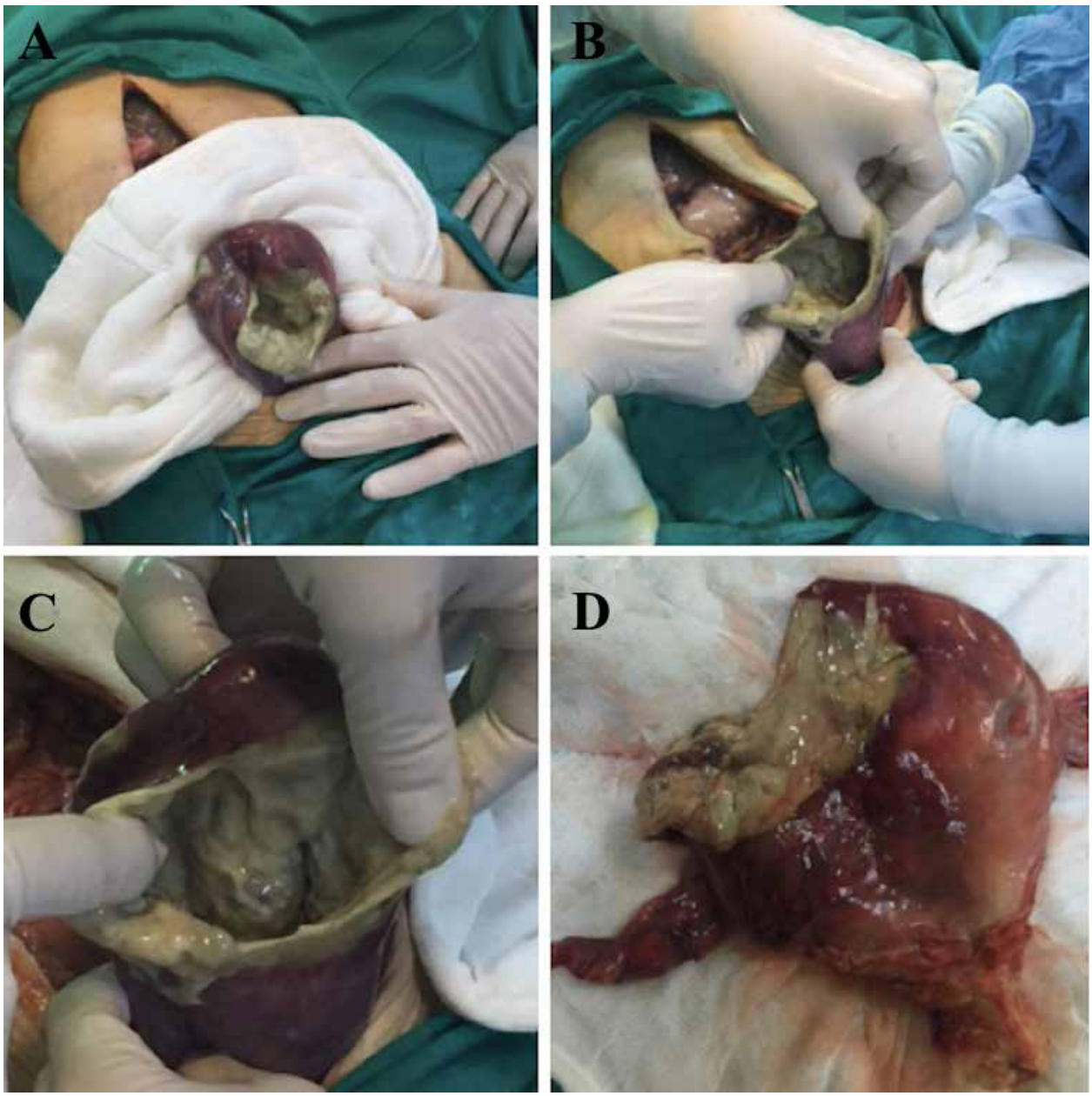

Fig 2: Intra-operative view of the uterine rupture

a 10 cm mass consistent with an abscess neighboring the bladder was detected (Figure 1). The patient underwent laparotomy with the diagnosis of acute abdomen, and approximately 1500-2000 cc purulent material was drained. Surgical exploration revealed no gastrointestinal perforation or pathology; however, the uterus was larger than normal, perforated from the fundus, and filled with pus-like fluid collection (Figure 2). Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed with the diagnosis of spontaneous pyometrium rupture. Following intra-abdominal irrigation and insertion of a drain, the patient was followed up in the intensive care unit with the diagnosis of septic shock. Dopamine infusion was administered to the patient who was put under mechanical ventilation. *Enterococcus faecalis* was detected in the culture of the fluid sampled from the intra-abdominal region. Piperacillin/tazobactam (Tazocin™) 4.5 g intravenously every eight hours and metronidazole (Flagyl®) 500 mg intravenously every eight hours were initiated as antibiotherapy. The patient died of septic shock and multiple organ failure on postoperative day 15 in the intensive care unit.

DISCUSSION

The number of patients with pelvic organ prolapse has been increasing with the increasing life expectancy of the general population. The age and systemic diseases of patients affect the type of surgery preferred in prolapse surgery. LeFort colpocleisis is a reliable surgery that may be performed using regional or local anesthesia in patients with total prolapse and cuff prolapse. The drainage of secretions must be aimed when performing LeFort colpocleisis in patients with a total uterine prolapse. This may be possible with partial LeFort colpocleisis surgery, in which the lateral sulci are open and drainage is possible.

Endometrial thickness is important when diagnosing endometrial pathologies in postmenopausal patients, and must be monitored regularly. Researchers suggest that premenopausal endometrium was more resistant against infections owing to cyclic discharge, and this resistance is broken in the postmenopausal period[7]. Pyometrium is more frequent in the postmenopausal patient group with a rate of 13.6%. Although many benign gynecologic pathologies and surgical interventions may cause cervical stenosis which may lead to pyometrium, gynecologic malignancies or radiotherapy may also cause cervical stenosis and pus accumulation within the uterus. The causes of cervical stenosis may be detected as senile cervicitis or gynecologic malignancy; however, other benign pathologies must be ruled out[8].

The main symptoms of patients with pyometrium were reported to be abdominal pain in 80%, fever in 45%, and vaginal discharge in 25%[9,10]. Abdominal pain, vaginal discharge and symptoms of acute abdomen were observed in our case, and the patient was in septic shock. Researchers have reported leukocytosis in 75% of patients with pyometrium; however, the initial white cell count was 12.6×10^9/L in our patient[9]. Hypoalbuminemia was detected in 88% of previous cases, and similarly, we detected hypoalbuminemia in our patient.

Pneumoperitoneum may be detected in 47-56% of pyometrium ruptures; pneumoperitoneum was detected in the abdominal CT of our patient[3,4]. Although the cause of pneumoperitoneum may be microorganisms producing gas, it might also be due to the transition of air from the genital tract to the peritoneal cavity[6]. Preoperative ultrasonography, magnetic resonance imaging and CT are instruments that facilitate the diagnosis. Almost half (47.4%) of patients with pyometrium are initially diagnosed as having peritonitis, 47.4% as having pneumoperitoneum and 36.8% as having gastrointestinal system perforation. Only 15.8% of cases may be diagnosed with pyometrium rupture preoperatively[3]. The treatment of pyometrium in the first phase must be drainage and antibiotherapy, after ruling out malignancy[11]. Hysterectomy must be evaluated as a treatment option in postmenopausal patients because pyometrium is asymptomatic in more than half of the patients, and spontaneous rupture has a mortality risk of 38%. Drainage, rupture repair and antibiotherapy may be attempted in younger patients who are planning future pregnancy[3]. Acute suppurative necrotizing endometritis with abscess formation, full thickness necrosis of the uterus, and serositis have been observed in histopathologic studies of ruptured uteri[5].

The patient died of septic shock and multiple organ failure on day 15 in the intensive care unit. The treatment of nine patients out of 22 cases of spontaneous pyometrium ruptures resulted with death in the review of Yıldızhan *et al*[3].

CONCLUSION

In conclusion, the pathologies causing pyometrium must be investigated and treated. Trans-vaginal ultrasonographic evaluation of the endometrium in postmenopausal patients, and monitoring of the uterine cavity gain importance in the diagnosis of pyometrium. Drainage of uterine secretions must be enabled in uterus-sparing LeFort colpocleisis cases. Spontaneous pyometrium rupture must be eliminated through drainage, antibiotherapy and hysterectomy in patients with pyometrium, when required, due to the high rates of mortality and morbidity associated with this condition.

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The authors declare that there is no conflict of interest regarding the publication of article.

REFERENCES

1. Sharma N, Singh AS, Bhaphiralyne W. Spontaneous perforation of pyometra. J Menopausal Med 2016; 22(1):47-49.
2. Malvadkar SM, Malvadkar MS, Domkundwar SV, Mohd S. Spontaneous rupture of pyometra causing peritonitis in elderly female diagnosed on dynamic transvaginal ultrasound. Case Rep Radiol 2016; 2016:1738521.
3. Yıldızhan B, Uyar E, Sismanoğlu A, Gulluoglu G, Kavak ZN. Spontaneous perforation of pyometra. Infect Dis Obstet Gynecol 2006; 2006:26786.
4. Patil V, Patil LS, Shiragur S, Ichalakaranji R. Spontaneous rupture of pyometra - A rare cause of peritonitis in elderly female. J Clin Diagn Res 2013; 7(8):1735-1736.
5. Stunell H, Hou D, Finlayson S, Harris AC. Spontaneous perforation of pyometra due to acute necrotising endometritis. J Obstet Gynecol 2011; 31(7):673-674.

6. Shapey IM, Nasser T, Dickens P, Haldar M, Solkar MH. Spontaneously perforated pyometra: an unusual cause of acute abdomen and pneumoperitoneum. Ann R Coll Surg Engl 2012; 94(8):e246-e248.
7. Shahid N, Khan H, Onon TS. Perforation of pyometra leading to diffuse peritonitis is not necessarily iatrogenics. J Obstet Gynaecol 2006; 26(1):76-77.
8. Vyas S, Kumar A, Prakash M, Kapoor R, Kumar P, Khandelwal N. Spontaneous perforation of pyometra in a cervical cancer patient. A case report and literature review. Cancer Imaging 2009; 9(1):12-14.
9. Ou YC, Lan KC, Lin H, Tsai CC, ChangChien CC. Clinical characteristics of perforated pyometra and impeding perforation: Specific issues in gynecological emergency. J Obstet Gynaecol Res 2010; 36(3):661-666.
10. Geranpayeh L, Fadaei-Araghi M, Shakiba B. Spontaneus uterine perforation due to pyometra presenting as acute abdomen. Infect Dis Obstet Gynecol 2006; 2006:60276.
11. Yousefi Z, Sharifi N, Morshedy M. Spontaneus uterine perforation caused by pyometra: A case report. Iran Red Crescent Med J 2014; 16(9):e14491.

Case Report

Inadvertently placed pacemaker lead into the left ventricle without thromboembolic complication: Due to Dabigatran or chance?

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ABSTRACT

A pacemaker lead implanted inadvertently into the left ventricle is a major risk factor for thromboembolic complications. Although warfarin has traditionally been used in the management of this complication, it has many limitations. We herein describe a case of an 83-year-old woman with history of chronic atrial fibrillation. The patient had undergone a permanent pacemaker implantation one year ago, which was later on proven to have the lead misplaced into the left ventricle. Pacemaker lead malposition was recognized incidentally one year after the implantation. We assumed that a novel oral anticoagulant dabigatran therapy used for chronic atrial fibrillation protected the patient from systemic embolic complications. The case seems to be significant in demonstrating the efficacy of dabigatran in terms of thromboembolism prevention due to inadvertent left ventricle placement of a pacemaker lead.

KEY WORDS: lead malposition, novel oral anticoagulant, thromboembolism

INTRODUCTION

Malposition of a pacemaker lead into the left ventricular cavity is unusual and potentially carries the risk for cardiac device-related complication[1]. In the presence of atrial septal defect, ventricular septal defect, and patent foramen ovale, the pacemaker lead can be placed unintentionally into the left ventricle during the pacemaker implantation procedure[2]. The major risk that is attributed to inadvertent pacemaker lead placement into the left ventricle is thromboembolic events. Thromboembolic events are frequently associated with this complication[3].

Although warfarin is an established anticoagulant in the management of left ventricular pacemaker lead placement, there has been no report on the usage of dabigatran, a novel oral anticoagulant, for this complication. To the best of our knowledge, the presented case is the first in the literature, where a misplaced pacing lead into the left ventricle led to no ischemic event for one year in a patient on dabigatran therapy.

CASE REPORT

An 83-year-old woman who had a history of permanent pacemaker implantation and chronic atrial fibrillation was admitted to our outpatient clinic for a routine check-up. Her creatinine clearance was 47 mL/min according to Cockcroft-Gault formula. She had been taking dabigatran therapy (110 mg twice a day) for three years. Due to a history of substantial fluctuations in the international normalized ratio, warfarin treatment had been withdrawn. The patient had undergone a permanent single chamber pacemaker (Medtronic) implantation at another institution one year ago for slow atrial fibrillation. Physical examination was not contributory. An electrocardiogram (ECG) showed paced complexes with right bundle branch block (RBBB) like configuration and a background

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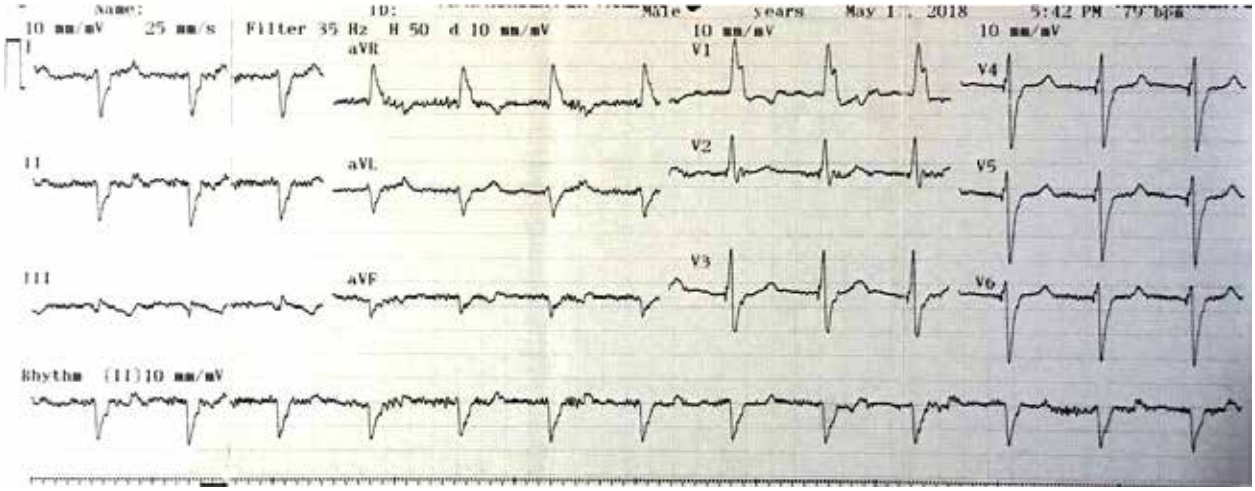

Fig 1: 12-lead electrocardiograph revealing right bundle branch block (RBBB) type paced QRS complexes and a basal rhythm atrial fibrillation.

rhythm of atrial fibrillation (Fig. 1). Chest radiography revealed the ventricular lead located more posteriorly, which led us to suspect a mal-placed ventricular lead (Fig. 2a, 2b). The transthoracic and transesophageal echocardiographic examinations show the pacemaker lead traversing the inter-atrial septum across the mitral valve and implanted in the lateral wall of the left ventricle (Fig. 3). No attached masses were detected. The pacing threshold, impedance and sensing parameters were all normal during the pacemaker follow-up. She had an uneventful course without any evidence of neurological deficiency or peripheral embolic phenomena for one year during dabigatran therapy. Based on the patient's renal function and age, dabigatran therapy was continued for a dosage of 110 mg twice daily.

DISCUSSION

Inadvertent placement of a pacemaker lead into the left ventricle is a rare complication that might be overlooked during the limited routine pacemaker interrogation. The RBBB pattern on the ECG is a useful clue to suspect inadvertent pacing lead misplacement. The RBBB pattern could also be seen in some septal true right ventricle pacing[4]. In our case, ECG showed a RBBB pattern of paced rhythm. Although ECG and chest radiography give rise to the suspicion of left ventricular lead placement, neither can precisely diagnose the pacemaker lead malposition. Transthoracic and transesophageal echocardiography were performed to confirm the diagnosis.

The most feared complication of left ventricle lead implantation is systemic thromboembolism, which

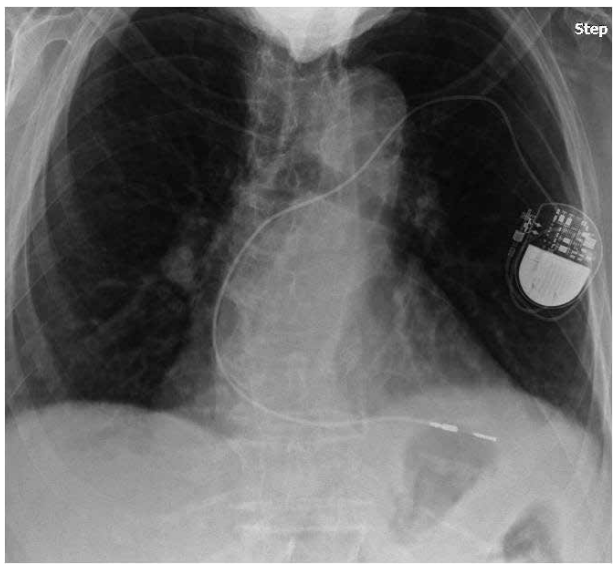

Fig 2a: Anteroposterior chest X-ray of a malpositioned left ventricular lead.

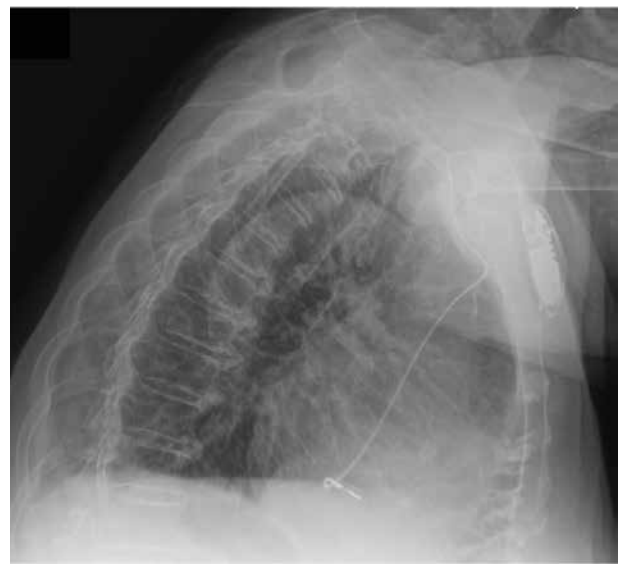

Fig 2b: Lateral chest X-ray of same patient. The pacemaker lead is located posteriorly, indicating a malpositioned ventricular lead.

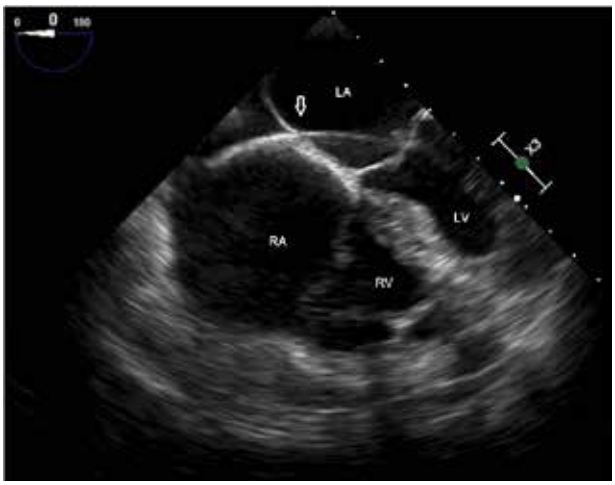

Fig 3: Two-dimensional transesophageal echocardiographic view showing the transit of the pacemaker lead across atrial septal defect (arrow) and its passage from left atrium into the left ventricle. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

may occur in approximately 40% of the patients[5]. There are different strategies to manage misplaced left ventricle lead implantation. The implantation duration is the main factor that may affect treatment strategies. When the diagnosis of inadvertent lead malposition is made early, the management of this complication is to reposition the lead in the right ventricle. Long-life anticoagulation with warfarin is an option when the diagnosis is delayed, as lead removal may be difficult and complicated by systemic embolization[6]. Although warfarin has traditionally been used in the management of this complication, it has many clinical limitations, such as multiple food and drug interactions, and narrow therapeutic range. Dabigatran, which is an oral direct thrombin inhibitor, is currently indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation[7]. Due to uneventful course for one year without any evidence of embolic events by the usage of dabigatran and the patient's history of labile international normalized ratio values, we decided to continue treatment with dabigatran instead of warfarin therapy. We assumed that the absence of thrombotic material and embolic complications may be attributed to the patient's dabigatran usage for chronic atrial fibrillation.

CONCLUSION

This case demonstrates that dabigatran may be an effective agent in prevention of thromboembolism in patients with a pacemaker lead that is inadvertently implanted into the left ventricle. However, our finding should be confirmed by a larger cohort.

ACKNOWLEDGMENT

Conflict of Interest: None.

REFERENCES

1. Ohlow MA, Roos M, Lauer B, Von Korn H, Geller JC. Incidence, predictors, and outcome of inadvertent malposition of transvenous pacing or defibrillation lead in the left heart. Europace 2016; 18(7):1049-1054.
2. Van Gelder BM, Bracke FA, Oto A, Yildirir A, Haas PC, Seger JJ, *et al*. Diagnosis and management of inadvertently placed pacing and ICD leads in the left ventricle: A multicenter experience and review of the literature. Pacing Clin Electrophysiol 2000; 23(5):877-883.
3. Agnelli D, Ferrari A, Saltafossi D, Falcone C. [A cardiac embolic stroke due to malposition of the pacemaker lead in the left ventricle. A case report]. Ital Heart J Suppl 2000; 1(1):122-125. [Article in Itlalian]
4. Yang YN, Yin WH, Young MS. Safe right bundle branch block pattern during permanent right ventricular pacing. J Electrocardiol 2003; 36(1):67-71.
5. Sharifi M, Sorkin R, Sharifi V, Lakier JB. Inadvertent malposition of a transvenous-inserted pacing lead in the left ventricular chamber. Am J Cardiol 1995; 76(1):92-95.
6. McManus DD, Mattei ML, Rose K, Rashkin J, Rosenthal LS. Inadvertent lead placement in the left ventricle: A case report and brief review. Indian Pacing Electrophysiol J 2009; 9(4):224-228.
7. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the ESC Guidelines for the 2010 management of atrial fibrillation developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33(21):2719-2747.

Case Report

Lymphoepithelioma-like carcinoma of the urinary bladder: Cases report and pooled analysis of 13 Chinese cases

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ABSTRACT

Lymphoepithelioma-like carcinoma of the urinary bladder (LELCB) is a rare type of malignant urothelial tumor. We report two cases of primary LELCB, and retrospectively collect all the reported primary LELCB cases in the Chinese population by searching English and Chinese databases. We also attempt to make recommendations to establish the prevention and treatment of LELCB. Thirteen patients with LELCB have been included till 2016, including the two cases we reported. Primary surgical treatments, adjuvant therapy or systemic chemotherapy were performed. This study would show the general features of LELCB. Finally, we conclude that conservative treatment with chemotherapy seems to be an option for pure and predominant LELCB cases.

KEY WORDS: bladder, lymphoepithelioma-like carcinoma, outcome, pathology

INTRODUCTION

Lymphoepithelioma-like carcinoma of the urinary bladder (LELCB) is a rare type of malignant urothelial tumor, characterized by a dense inflammatory infiltrate. The first case was described by Zukerberg in 1991[1]. LELCB presents a reported incidence of 0.3-1.3% of all bladder cancers, which is much higher in males[2]. In the urinary tract, LELCB typically occurs in the site of bladder, in spite of isolated cases in the renal pelvis, ureter and urethra[3,4]. Lymphoepithelioma-like carcinoma is initially described in the nasopharynx, and the Epstein–Barr virus (EBV) seems to play a key role in its development[5]. Contrary to this, the presence of EBV has not been detected in LELCB[6].

Due to the tiny number of cases presented in literature, no clear guideline recommendations could be established for the ideal prevention and treatment of LELCB. Furthermore, it is imperative to differentiate between LELCB and transitional cell carcinoma, because it has implications for prognosis and treatment. Therefore, we presented our two cases and carried out a pooled analysis of all the reported Chinese cases to clarify the clinical and therapeutic features.

CASE REPORT

Case 1

A 73-year-old man was admitted to our department with the chief complaint of macroscopic hematuria for two months. There was a medical history of hypertension treated with amlodipine, but no history of urological problems. Physical examination and vital signs were unremarkable. A computed tomography scan revealed a ureteral orifice tumor 6 cm in diameter with perivesical tissue invasion and right hydronephrosis. Cystoscopic examination together with bladder biopsy was performed and finally demonstrated high grade urothelial carcinoma of the bladder. The patient underwent partial cystectomy (PC) and right

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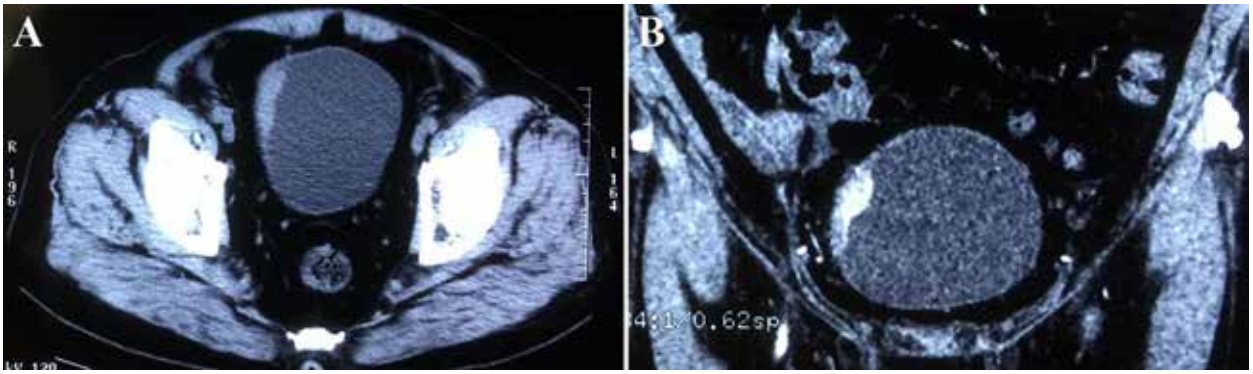

Fig 1: Computed tomography scans indicated a thickened right bladder wall and the tumor had spread into the deep bladder wall layer.

ureterovesical reimplantation. Histopathological examination revealed a 6x3x2 cm lymphoepithelioma-like carcinoma with perivesical tissue invasion (T3N0). The immunohistochemical examination showed positive for CK (pan) (+++), EGFR (+++), p53 (++), p170 (++), GSTπ (++) and negative for EBV-encoded RNAs (-), confirming the diagnosis of LELCB. The patient then received a concurrent chemotherapy regimen; including gemcitabine administered at 1000 mg/m^2 on days 1 and 8 and cisplatin 70 mg/m^2 on day 1 of a 21-day cycle. The patient could tolerate this regimen well. He has been without recurrence or metastasis for 24 months after operation, and currently is on follow-up.

Case 2

The patient was an 84-year-old man with macroscopic hematuria for 10 days. He had a history of transurethral prostatectomy for 10 years. Comorbidities included hypertension and diabetes. Physical examination and vital signs were unremarkable. Computed tomography scan demonstrated a thickened right bladder wall (1.4 cm), possible metastatic tumor (Figure 1). Cystoscope was unsuccessful due to urethral stenosis. PC was finally performed and histopathological examination revealed a 4.5x3.5x2 cm LELCB (T3N0). Immunostaining results included CK (pan) (+++), CK20 (-), Ki67 (50% +), EBV-encoded RNAs (-), CK (H) (+++), p63(+++), and CD20 (B cells ++) (Figure 2). The chemotherapy regimen was the same as mentioned above. At the time of writing this report, the patient is under observation with regular clinical follow-up and remains well after 13 months, without evidence of tumor recurrence.

Reported Chinese LELCB cases and pooled analysis

Cases and methods

LELCB were classified as a distinct variant of urothelial carcinomas in the WHO classification of urothelial tumors in 2004[7]. It was first described in 1991 and only a few cases have been reported till now, hindering the diagnosis and treatment for this rare type of carcinoma. To the best of our knowledge, the present study is the first pooled analysis of LELCB in Chinese patients, providing the outline of clinical and therapeutic features.

We retrospectively collected all the reported primary LELCB cases in the Chinese population by searching the following English and Chinese databases: PubMed, China National Knowledge Infrastructure, Chinese Scientific Journals and Wanfang Data. Totally,

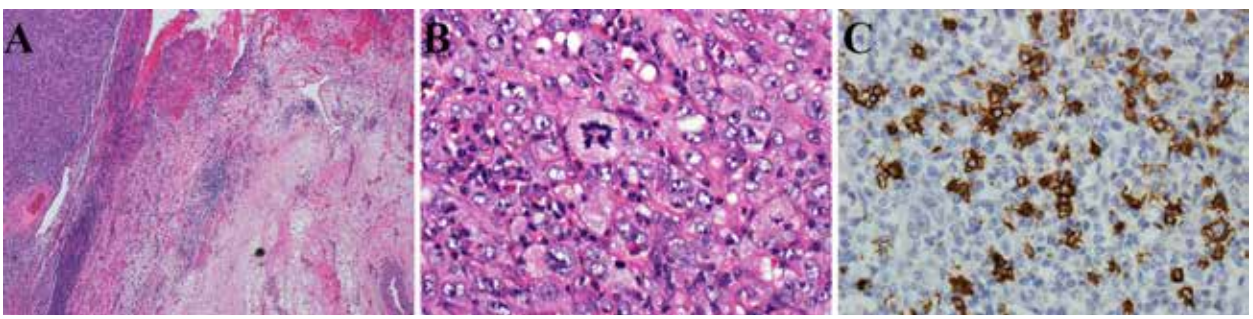

Fig 2: Pathological findings **(A)** Lymphoepithelioma-like carcinoma, syncytial pattern with prominent lymphocytic infiltrate (hematoxylin and eosin x200); **(B)** Lymphoepithelioma-like carcinoma with urothelial carcinoma (hematoxylin and eosin x400); **(C)** Positive staining with antibodies against CD20 showed less B-lymphocytes (x400).

Table 1: Reported cases of lymphoepithelioma-like carcinoma of urinary bladder reported from mainland China and Taiwan.

Reference	Case	Years	Gender	Age (year)	Tumor size (cm)	Stage	Pathology	Primary treatment	Follow-up (month)	Outcomes
Chen *et al*[12]	1	2005	M	73	3×2	T3	LELC	RC, CH(MVAC)	26	TS
	2	2005	M	63	UA	T1	LELC	TURBT, CH(MVAC)	16	TR
Ye *et al*[13]	3	2006	M	74	1.0×1.0×0.7	UA	LELC, urothelial cell carcinoma	PC	UA	UA
Wu *et al*[17]	4	2009	M	75	4×2×2	UA	LELC	PC, BI(mitomycin)	21	TS
	5	2009	F	62	3×2×2	T2	LELC	PC, BI(mitomycin)	19	TR
Luo *et al*[14]	6	2009	M	81	5×4.3×3.2	T3	LELC	PC	UA	TS
	7	2009	F	68	2.5×2.2×2.0	T2	LELC	PC	84	TR
Chou *et al*[18]	8	2012	M	71	2×2	T2	LELC	TURBT, BI (BCG)	6	TR
Pan *et al*[19]	9	2013	UA	UA	UA	UA	LELC	RC, CH(UA)	6	TS
	10	2013	UA	UA	UA	UA	LELC	TURBT, CH(UA)	6	TS
Zhang et al[20]	11	2014	M	66	2.0×2.0×1.5	T2	LELC, adenocarcinoma	RC, OIN, BI(gemcitabine)	18	TS
Our case	12	2016	M	73	6×3×2.5	T3	LELC	PC, CH(GC)	24	TS
	13	2016	M	84	4.5×3.5×2	T3	LELC	PC, CH(GC)	13	TS

F: female; M: male; BCG: Bacillus Calmette-Guerin; BI: bladder instillation; CH: chemotherapy; GC: gemcitabine-cisplatin; LELC: lymphoepithelioma-like carcinoma; MVAC: methotrexate-vinblastine-doxorubicin-cisplatin; OIN: orthotopic ileal neobladder; PC: partial cystectomy; RC: radical cystoprostatectomy; TURBT: transurethral resection of bladder tumor; TS: tumor-free survival; TR: tumor recurrence; UA: unavailable.

13 patients have been documented till 2016, including the two cases reported here (Table 1). Patients were evaluated for age, sex, tumor size, local pathological staging, histological subtype, primary and/or adjuvant treatments, follow-up period and outcomes. In addition, the positive results of immunohistochemical studies for cytokeratin and lymphoid markers were also summarized. Parts of data were missed and to get maximum information, these indicators were demonstrated by analyzing all the available data. Primary treatments included transurethral resection of bladder tumor (TURBT), PC or radical cystectomy. Adjuvant treatments, if performed, included three to five courses of systemic multiagent chemotherapy. Histological subtype for LELCB was according to the classification of Amin *et al*[8]. Mixed LELCB included

Table 2: Positive immunostaining markers of LELCB

Reference	Chen *et al*[12]	Ye *et al*[13]	Wu *et al*[17]		Luo *et al*[14]		Chou *et al*[18]	Pan *et al*[19]		Zhang *et al*[20]	Our cases	
Cases	1	1	1	2	1	2	1	1	2	1	1	2
Years	2005	2006	2009	2009	2009	2009	2012	2013	2013	2014	2016	2016
Available	UA							UA	UA			
Positive markers (tumor cells)		AE1/AE3			AE1/AE3	AE1/AE3	AE1/AE3					
			EMA		EMA	EMA						
		CAM5.2										
										CK5/6		
		CK7			CK7	CK7						
					CK8	CK8						
											CK(pan)	CK(pan)
			L-CK	L-CK								
										H-CK		H-CK
											EGFR	
				Ki-67								Ki-67
					P53	P53					P53	
										P63		P63
											P170	
										GSTπ		
Positive markers (lymphocytes)		CD3			CD3	CD3				CD3		
			CD19									
		CD20			CD20	CD20				CD20		CD20
					CD45	CD45				CD45		
				LCA								

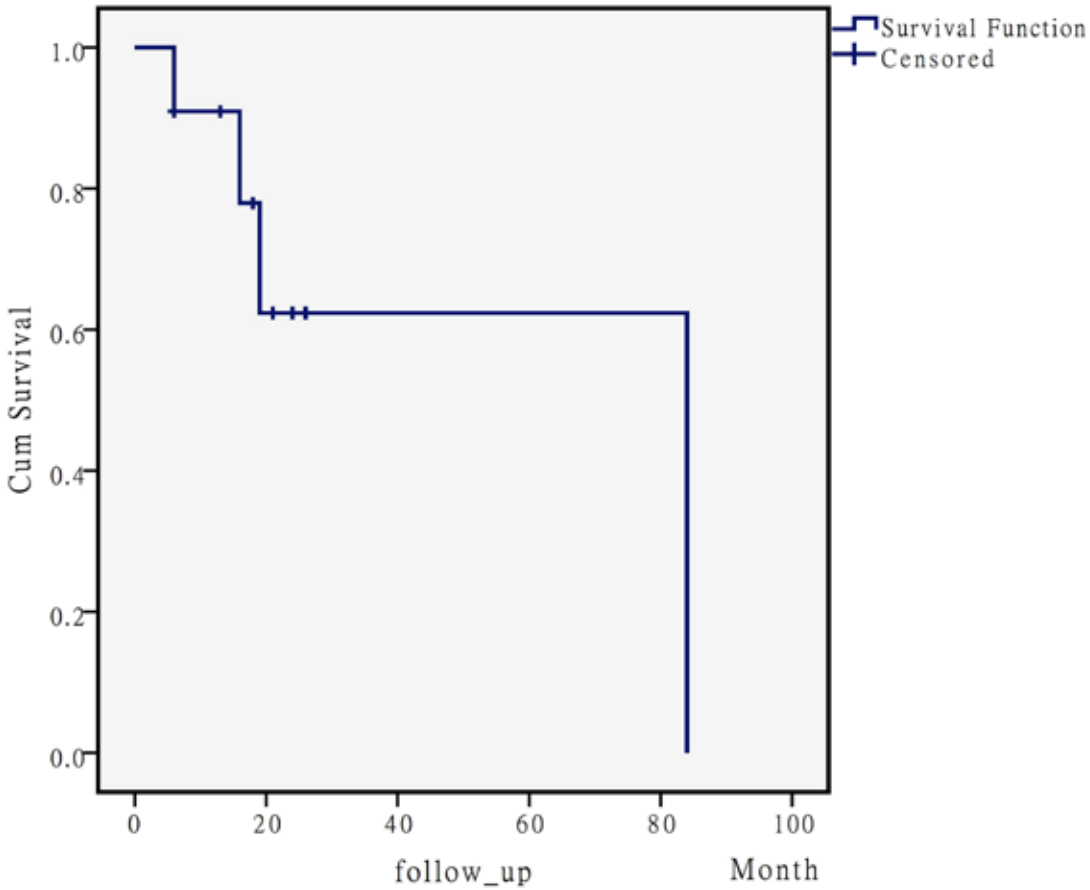

Fig 3: The Kaplan-Meier survival curve of all reported Chinese cases of lymphoepithelioma-like carcinoma of bladder.

the predominant and focal subtypes which were demonstrated for associated bladder tumors, including low or high grade transitional cell carcinoma, adenocarcinoma or squamous cell carcinoma. Measurement of the overall survival period began at the time of surgery. Tumor recurrence due to LELCB was the only endpoint considered as the purpose of this study. The survival curves were drawn using the Kaplan-Meier method. Due to the small LELCB population, univariate and multivariate analyses were not performed.

Results of pooled analysis

As shown in Table 1, 13 Chinese patients with primary LELCB were collected from literature till 2016. By analyzing all the available data, we concluded the characteristics of the overall patients as follows. LELCB mainly occurred in male patients and the male to female ratio was 9:2. The mean age at diagnosis was 71.8 years (range: 63-84 years). The tumor sizes were mainly below 4 cm in diameter (60%), and nearly all available cases showed T2 stage and above (88.9%). LELCB histological subtypes resulted pure in 11 cases (84.6%) and mixed in two cases (15.4%), respectively. Primary surgical treatments included TURBT in three cases (23.1%), PC in seven (53.8%), and radical cystectomy in three (23.1%). Adjuvant therapy was performed in 10 patients (76.9%), including systemic chemotherapy in seven and intravesical chemotherapy in three. These reviewed patients were followed up for a median of 21.7 months (range: 6-84 months). For the outcomes of the 12 available patients, four patients (33.3%) showed tumor recurrence while eight (66.7%) were alive without evidence of recurrence. Particularly, seven of 11 patients (63.6%) with pure LELCB did not show evidence of disease.

Table 2 demonstrates the positive immunostaining results for cytokeratin and lymphoid makers of all LELCB cases. The epithelial component presented positive staining for epithelial membrane antigen and several cytokeratins including AE1/AE3, CK7 and CK8, while the lymphocyte population was positive for CD3 and CD20.

Figure 3 shows the overall survival curves of the 12 available patients with primary LELCB. Totally,

tumor recurrence occurred at a median 17.5-month follow-up post primary surgery.

DISCUSSION

LELCB is a rare type of urothelial carcinoma, and the certain cause for it remains enigmatic. The lymphoepithelioma-like carcinoma was originally described in nasopharynx, which is particularly prevalent in Southeastern Asia and strongly associated with EBV infection. However, EBV was not identified in any Chinese LELCB cases based on our pooled analysis. The same situation is also present in Caucasian population, suggesting no racial or geographical differentiation[6,9-11]. Chen *et al* first detected EBV in two Chinese LELCB cases and demonstrated the absence of EBV-encoded RNAs in the tumor cell using in situ hybridization[12]. Consistently, Ye *et al*'s study[13] and ours also showed negative results of EBV for LELCB. Different from EBV, high expression of p53 may be a possible risk factor for LELCB[4,13-15]. In many high grade and aggressive bladder carcinomas, the p53 gene is mutated, overexpressed and highly localized to the nucleus, where it is rapidly degraded[16]. Intensely and widely positive for p53 protein using immunohistochemistry was noted previously in LELCB of Chinese[13,14] and other populations[4,15]. One of our cases also supports the existence of high expression of p53. However, it does not seem related to either p53 mutation or EBV infection or integration. Further studies are needed to explore the relationship between p53 and LELCB.

Our pooled study revealed that LELCB primarily affected the elderly with male predominance. The mean age at LELCB diagnosis seems to be older in Chinese populations than in other races[2,10,17-20]. With respect to chief complaint, the principal symptoms of LELCB in Chinese patients were mostly macroscopic hematuria with or without irritative voiding disorders, which is consistent with other studies involving different races[2,10,17-20]. This clinical presentation does not differ from common urothelial carcinomas. Chinese LELCB often manifested in T2-T3 stages with small tumors (below 4 cm), regardless of histological classification. The metastatic potential of LELCB seems to be low and it is usually diagnosed at less advanced stages with a more favorable long-term prognosis than other types of undifferentiated invasive bladder cancer. These features in Chinese cases are quite similar to those in other populations, when compared with the pooled results of dozens of LELCB by Yoshino *et al*[2]. As shown in their study, LELCB patients with T2-T3 accounted for 83% of the pooled patient population, and 67% of the overall patients did not show any evidence of disease (66.7% in our study) with a cause-specific survival rate of 83%.

The histological features of LELCB included an undifferentiated epithelial tumor with significant lymphocytic infiltration; the syncytial arrangement of large neoplastic ephithelial cells with prominent nuclei and nucleoli can also been observed[15]. These features can also be seen in Chinese cases[14]. Amin *et al* subdivided LELCB into pure (100%), predominant (>50%) and focal (<50%) depending on the lymphoepithelioma component[8]. The improved awareness of LELCB is important, because a correct diagnosis has prognostic and therapeutic implications. The differential diagnosis mainly includes chronic cystitis, malignant lymphoma, and undifferentiated urothelial carcinoma, all of which may show similar histological appearances. These can be excluded by relevant immunohistochemistry for both epithelial and lymphocytic tumor constituents. As shown by Table 2, identification of epithelial markers, such as epithelial membrane antigen and several cytokeratins (AE1/AE3, CK7 and CK8, etc.), is critical to confirm the epithelial origin of the LELCB and to exclude other possible diagnosis like lymphoma. Additionally, a primary tumor in nasopharynx should be excluded when LELCB is identified. Some studies demonstrated that LELCB of pure or predominant types had a relatively favorable prognosis, while the prognosis of focal one was quite poor[6].

Since LELCB is a rare disease, very few cases have been reported in the literature. No clear guideline has been established for LELCB treatment. As shown by this pooled analysis, TURBT or PC was generally performed as local therapy, and radical cystectomy was only performed in three patients; chemotherapy was usually performed following primary surgical treatment. The pathological form of our cases was pure type, and both underwent PC followed by cisplatin-based chemotherapy. It has been suggested that pure and predominant LELCB is sensitive to chemotherapy and may be better treated with conservative treatment. In our pooled study, 11 of 13 were pure LELCB and showed a relatively longer recurrence-free survival period. This result was in parallel with Yoshino *et al*'s pooled analysis, which indicated that the cause-specific survival rate was more than 90% for both pure and predominant LELCB[2]. The better prognosis of pure types may be related to the importance of the inflammatory infiltrate and cytotoxic T lymphocytes for two causes: early onset of symptoms leading patients to seek care, and strengthening the action of chemotherapeutic agents[7]. Due to the lack of sufficient cases, clear risk factors could not be demonstrated for Chinese LELCB. However, to some extent, female

gender seems at higher risk of tumor recurrence compared to males. Tumor recurrence was seen in both available female patients of our review, whereas it occurred only in two of eight males.

CONCLUSION

LELCB is a rare type of bladder tumor without therapeutic consensus. This pooled analysis has shown the general features of Chinese cases and is a necessary complement to the current knowledge of LELCB. Together with other LELCB case reports, our study indicates that conservative treatment (TURBT in particular) with chemotherapy seems to be an option for pure and predominant LELCB cases. The clinicians should improve the awareness of LELCB and further accumulation of data is needed.

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Competing interests: The authors declare that they have no competing interests.

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REFERENCES

1. Zukerberg LR, Harris NL, Young RH. Carcinomas of the urinary bladder simulating malignant lymphoma. A report of five cases. Am J Surg Pathol 1991; 15(6):569-576.
2. Yoshino T, Ohara S, Moriyama H. Lymphoepithelioma-like carcinoma of the urinary bladder: A case report and review of the literature. BMC Res Notes 2014; 7:779.
3. Cohen RJ, Stanley JC, Dawkins HJ. Lymphoepithelioma-like carcinoma of the renal pelvis. Pathology 1999; 31(4):434-435.
4. Izquierdo-Garcia FM, Garcia-Diez F, Fernandez I, *et al*. Lymphoepithelioma-like carcinoma of the bladder: three cases with clinicopathological and p53 protein expression study. Virchows Archiv 2004; 444(5):420-425.
5. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol 1995; 103(3):308-315.
6. Kushida N, Kushakabe T, Kataoka M, Kumagai S, Aikawa K, Kojima Y. External beam radiotherapy for focal lymphoepithelioma-like carcinoma in the urinary bladder: A case report and literature review. Case Rep Oncol 2015; 8(1):15-20.
7. Ziouziou I, Karmouni T, El Khader K, Koutani A, Andaloussi AIA. Lymphoepithelioma-like carcinoma of the bladder: A case report. J Med Case Rep 2014; 8:424.
8. Amin MB, Ro JY, Lee KM, Ordonez NG, Dinney CP, Gulley ML, *et al*. Lymphoepithelioma-like carcinoma of the urinary bladder. Am J Surg Pathol 1994; 18(5):466-473.
9. Mori K, Ando T, Nomura T, Sato F, Mimata H. Lymphoepithelioma-like carcinoma of the bladder: A case report and review of the literature. Case Rep Urol 2013; 2013:356576.
10. Tamas EF, Nielsen ME, Schoenberg MP, Epstein JI. Lymphoepithelioma-like carcinoma of the urinary tract: A clinicopathological study of 30 pure and mixed cases. Mod Pathol 2007; 20(8):828-834.
11. Gulley ML, Amin MB, Nicholls JM, Banks PM, Ayala AG, Srigley JR, *et al*. Epstein-Barr virus is detected in undifferentiated nasopharyngeal carcinoma but not in lymphoepithelioma-like carcinoma of the urinary bladder. Hum Pathol 1995; 26(11):1207-1214.
12. Chen KC, Chiang HS, Fang CL. EBER expression of pure urinary bladder lymphoepithelioma-like carcinoma in two unique Asian patients. Urol Int 2005; 74(3):280-282.
13. Ye QL, Jin XL. Primary lymphoepithelioma-like carcinoma of the urinary bladder: A case report. Modern Journal of Integrated Traditional Chinese and Western Medicine 2006; 15:792-793.
14. Luo Q, Mao Y, Zhou J, Yuan J, Yang Y. Lymphoepithelioma-like carcinoma of the urinary bladder: a case report and review of the literature. Cancer Research on Prevention and Treatment 2009; 36:340-341.
15. Kozyrakis D, Petraki C, Prombonas I, Grigorakis A, Kanellis G, Malovrouvas D. Lymphoepithelioma-like bladder cancer: Clinicopathologic study of six cases. Int J Urol 2011; 18(10):731-734.
16. Esrig D, Elmajian D, Groshen S, Freeman JA, Stein JP, Chen SC, *et al*. Accumulation of nuclear p53 and tumor progression in bladder cancer. N Engl J Med 1994; 331(19):1259-1264.

17. Wu X, Yan X, Li Z, Yang S, Hu W, WS. Z. Primary lymphoepithelioma-like carcinoma of the urinary bladder: report of two cases. Chinese Journal of Urology 2009; 30:378.
18. Chou C, Yang S, Tzen C. Primary lymphoepithelioma-like carcinoma of the urinary bladder: Case report and literature review. Urological Science 2012; 23:125-128.
19. Pan ST, Wang RC, Liu MY, Chuang SS. Lymphoepithelioma-like carcinoma of the urinary bladder: A report of two cases. Anal Quant Cytopathol Histpathol 2013; 35(6):344-348.
20. Zhang R, Lu H, Qi X. Lymphoepithelioma-like carcinoma of the urinary bladder with adenocarcinoma component: A case report. Chinese Journal of Urology 2014; 35:550.

Case Report

Atypical presentation of herpes simplex encephalitis in a patient with bipolar disorder: A case report and literature review

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ABSTRACT

A few published reports suggest the possible co-occurrence of anti-N-methyl-D-aspartate receptor antibody encephalitis in patients with bipolar disorder who show atypical presentations of herpes encephalitis. We report an adult woman with a known case of bipolar 1 disorder who showed an atypical presentation of a depressive episode with psychosis and herpes simplex encephalitis. She did not improve with an adequate dose of psychotropic medications; instead, her condition continued to decline and she started to display signs of lethargy, agitation, confusion, memory deficits, word-finding difficulties, difficulty swallowing, disorganized behavior, and jerky movement. Her vital signs were normal and her neurological examination was unremarkable. Computer tomography and magnetic resonance imaging tests of her brain were normal. She developed a sudden fever and became disoriented. Cerebrospinal fluid results confirmed viral encephalitis, and she tested positive for herpes simplex virus type 1 DNA. Patients with known psychiatric disorders who show any unusual presentation of psychiatric features in combination with cognitive impairments, neurological symptoms, and abnormal movements should be investigated thoroughly for possible secondary psychiatric illness. A high index of suspicion for the underlying etiology, with a broad approach to test for infectious diseases and various neuronal autoantibodies, can prompt correct diagnosis and management.

KEY WORDS: anti-NMDAR encephalitis, autoimmune encephalitis, bipolar, herpes simplex encephalitis, Saudi

INTRODUCTION

Patients with bipolar disorder have a high premature mortality rate and a decreased life expectancy of 9-14 years[1]. Besides death from natural causes, these patients have increased rates of exposure to microbial agents and have abnormal levels of some immune markers[2]. Furthermore, diagnoses of medical illnesses and treatments can be clinically challenging, especially when these involve severe infections and autoimmune diseases that can present with encephalitis[3].

Encephalitis is an acute inflammation of the brain and can be a life-threatening condition, especially in children and patients older than 55 years[4]. Most cases are caused by viral infections (the most common being herpes simplex virus encephalitis) or autoimmune diseases (commonly reported as anti-N-methyl-D-aspartate receptor [anti-NMDAR] encephalitis)[5]. Patients may present with prominent psychiatric manifestations during the onset of encephalitis, which can lead to misdiagnosis of their primary mental disorder[5]. Early and correct diagnosis, coupled with proper therapy, may improve prognosis.

We report a patient with a known case of bipolar disorder who developed encephalitis that had remained undetected for too long. The aim of this case report is to highlight the difficulties that may arise in identifying the co-morbid presence of encephalitis in patients with bipolar disorder.

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CASE REPORT

The patient was a 43-year-old Saudi woman who had presented to a psychiatry clinic with her first episode of mania 20 years previously. A diagnosis of type 1 bipolar disorder was made. She had complete remission of her symptoms after a one-year treatment with lithium. However, she became euthymic and her medication was gradually stopped. Three years later, the patient presented with another manic episode with associated psychotic features (auditory and visual hallucinations, accompanied by paranoid and grandiose delusions) and lithium was resumed. The patient subsequently experienced frequent relapses with depressive or manic episodes, associated with psychotic features and was hospitalized six times. Despite adequate trials of several medications (lithium, sodium valproate, lamotrigine, fluvoxamine, fluoxetine, venlafaxine, mirtazapine, imipramine, nortriptyline, quetiapine, olanzapine, chlorpromazine and propranolol), she responded to treatment briefly or not at all. At her final outpatient psychiatric follow-up, which was five months prior to her last hospital admission, she was in a depressive episode and her medications were adjusted to 15 mg olanzapine, 40 mg propranolol, 80 mg fluoxetine and 800 mg lithium.

At the time of her last hospitalization, her mental condition had been worsening for two weeks. She reported a depressed mood; anhedonia; decreased drive and energy; feelings of worthlessness; insomnia and decreased quality of sleep; and psychomotor retardation. She was also suffering from psychotic symptoms, such as auditory and visual hallucinations associated with extreme fear and bizarre behavior related to her hallucinations. In addition, she had a history of reduced alertness and concentration, slowed thinking, forgetfulness, diarrhea, and anorexia. The patient was not aggressive or agitated. She had no history of substance abuse or of suicidal ideas or plans.

At the time of her admission to the psychiatric ward, the patient had the appearance of a woman older than her stated age, with fair hygiene and grooming, and a thin body build. She looked pale. She was calm and partially cooperative, but she frequently closed her eyes and made hallucinatory gestures. Her voice, speech and tone were low. She showed a lack of spontaneity, but she responded to questions with short answers that were coherent and relevant. She was depressed, her affect was restricted, and she had persecutory delusions. She displayed poverty of thought in her speech, and experienced visual and auditory hallucinations. Her judgment and insight were impaired. A physical examination indicated normal vital signs, as well as normal cardiovascular and pulmonary findings. A neurological examination revealed her to be alert and oriented, but her thinking was slow. Examinations of the cranial nerves, motor strength, sensory functions and gait were unremarkable apart from a coarse tremor in both hands.

An initial work-up in the emergency room included a complete blood count, a complete metabolic panel, and a thyroid-stimulating hormone test; all showed near-normal results except for a mild elevation of liver enzymes and creatinine levels, possibly caused by dehydration and poor nutrition. Her lithium level was 0.6 mmol/L, and a urine drug screen was negative. Brain computed tomography revealed no significant abnormalities. An electrocardiogram showed a normal sinus rhythm and QTc interval. She was admitted to the psychiatric ward categorized as a patient with bipolar disorder in a depressive episode with psychotic features and with a suspicion of lithium toxicity based on her symptoms and clinical signs (diarrhea, anorexia and coarse tremor). The treatment plan was to withhold lithium and other medications temporarily and to keep her on PRN medications for her agitation and insomnia.

During the first days of the patient's hospitalization, because her main symptoms were related to depression and psychosis, the regular dose of olanzapine was optimized to 25 mg, and 150 mg bupropion was added. One week later, the patient showed no improvement; on the contrary, she had deteriorated further. For this reason, her worsening symptoms were suspected to indicate another medical illness apart from her primary psychiatric illness. More work-up was therefore ordered to rule out thyroid disease, multiple sclerosis, Wilson's disease, and connective tissue diseases. All related laboratory results and cranial magnetic resonance imaging (MRI) under general anesthesia were unremarkable (Figure 1). At the end of the first week, her condition continued to decline, and she started to display signs of lethargy, agitation, confusion, memory deficits and word-finding difficulties. She also had difficulty swallowing and had jerky movement, with demonstrated worsening of her disorganized behavior.

A subsequent electroencephalogram (EEG) showed mild encephalopathy but no epileptiform discharges. Her medications were immediately stopped, and the investigations were repeated. A complete blood count showed an elevated white blood cell count of 21.3×10^9/L with predominant neutrophils of 15.9×10^9/L. A liver function test also showed an alanine amino transferase level of 248 units/L, and an aspartate aminotransferase level of 132 units/L. The patient also showed electrolyte disturbances; her creatinine level was 166 mg/dL and her sodium level was 154 mEq/L. Her level of creatine kinase was mildly raised at 197 U/L.

For the first time during this hospitalization, she developed a high-grade fever of 39 °C. She was

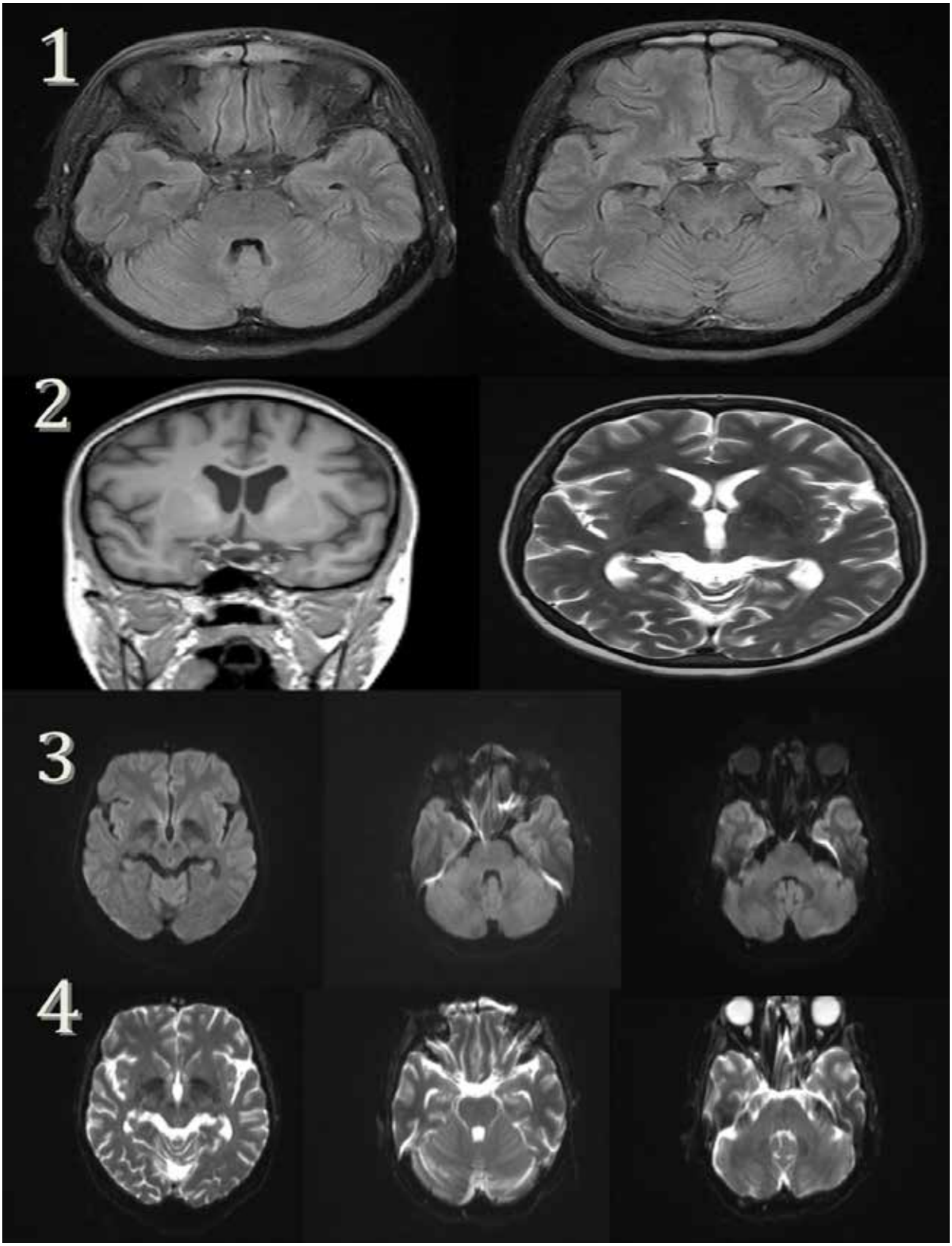

Fig 1: Multiplanar multi sequential MRI without IV contrast administration. Normal brain MRI. **(1)** FLAIR image MRI of the brain showed the normal signal intensity of medial aspect of temporal lobes and inferomedial aspect of frontal lobes. **(2)** Coronal T1 and axial T2 images showed the normal signal intensity of bilateral temporal lobes and insular cortices. **(3 & 4)** Diffusion-weighted imaging and apparent diffusion coefficient showed no abnormal restricted diffusion.

relocated to the intensive care unit due to autonomic instability and a decreased level of consciousness; her Glasgow Coma Scale score dropped from 13 to 7. A lumbar puncture was performed, which led to a positive diagnosis of infection with herpes simplex virus, type 1 (HSV-1). Her cerebrospinal fluid (CSF) glucose level was 5.2 mmol/L, protein was 0.4 mg/dL, white blood cell count was 1.0 cells/μL, red blood cell was 0.0 cells/μL, and lactate dehydrogenase was 34 units/L. No signs of other viral infections were evident. She did not respond to a trial of antiviral therapy (acyclovir). She developed a bilateral brain infarction due to hypotension and her Glasgow Coma Scale score deteriorated to 4. During the second week of hospitalization, the patient died due to cardiac arrest.

DISCUSSION

This was a challenging case with a few key points that deserve mention. First, this case centers on an adult woman with no known medical issues apart from a 20-year history of type 1 bipolar disorder who presented with relapse but with atypical symptoms. The major concern was the relation of these symptoms to her disorder. She had previously experienced visual and auditory hallucinations, according to her past psychiatric history. Second, lithium toxicity was suspected, which was initially based on the patient's clinical presentation (diarrhea, coarse tremor, dullness and memory deficits). Third, her diagnostic work-up included tests to rule out other possible illnesses, and her brain computed tomography and brain MRI were normal, although an EEG showed mild encephalopathy. Her vital signs were normal, and her neurological examination was unremarkable. However, her presentation did not conform to a typical relapse of bipolar disorder, as she showed de novo development of cognitive and kinetic symptoms. Eventually, she developed movement disorders, lethargy, disorientation, confusion, a decreasing level of consciousness, decreased motor response, and dysphagia, suggesting the probability of emergence of another co-morbid medical condition, especially encephalitis. Polymerase chain reaction testing of her CSF was positive for HSV-1 DNA, confirming viral encephalitis.

HSV encephalitis (HSE) is a rare disease with an annual incidence of 0.2-0.4/100,000 in the general population[6]. Approximately 80% of adult patients typically present with fever, while other symptoms can include confusion and disorientation (72%); personality changes and behavioral disturbances (59%); headache (58%); altered mentation (58%); focal neurological findings (41%; including cranial nerve deficits, hemiparesis, dysphasia, aphasia, or ataxia); and reduced levels of consciousness within a one-week period[7,8]. Brain MRI is the preferred imaging technique for patients with suspected HSE. The initial lesions are unilateral and classically involve the temporal and frontal regions of the brain.

MRI images typically highlight abnormalities in 95% of patients in those areas at the onset of infection after a median duration of three days of presentation of the neurological symptoms[9]. EEG results are abnormal in >80% of patients with HSE and most often display intermittent high amplitude slow waves, but the changes are nonspecific. The EEG pattern most characteristic of HSE consists of periodic lateralized epileptiform discharges that originate from the involved temporal lobe[10]. Typical CSF abnormalities include elevated protein levels (50-200 mg/dL or more) and a high white blood cell count (≥ 5-500 cells/mm^3), with a predominance of lymphocytes (60-98%, with a median of about 80%)[11].

As previously mentioned, our patient's presentation did not fit the typical presentation of HSE, and she did not respond to acyclovir therapy. Therefore, her presentation was not only atypical, but it was suggestive of an involvement of neuropathogenicity other than HSV, possibly anti-NMDAR encephalitis. Clinical diagnosis of anti-NMDAR encephalitis is particularly difficult, and this disease may show resistance to medical interventions if not started promptly[5]. A multi-institutional observational study conducted between 2007 and 2012 on 501 patients with anti-NMDAR encephalitis revealed that most of these patients responded to immunotherapy within 18 months[12].

The classic neuropsychiatric syndrome associated with anti-NMDAR encephalitis is well-described in multiple review studies[3,5,13-15]. About 80% of patients with anti-NMDAR encephalitis are young females[12]. Clinically, approximately 70% of these patients present with a prodrome of headache, fever, vomiting, diarrhea, and upper respiratory tract symptoms. In our case, the patient was dehydrated upon admission due to two weeks of anorexia and diarrhea. Typically, within two weeks from onset, prominent psychiatric symptoms and personality changes emerge. Cognitive changes, including impairment of attention, concentration and memory, lead to confusion that appears over time. During her hospitalization, our patient demonstrated all these changes. Later, she developed a movement disorder and exhibited language difficulty. She experienced fluctuations in mental status; her level of consciousness decreased along with rapid decline of responsiveness; and she was unable to follow verbal commands; all these symptoms are similar to those reported for anti-NMDAR encephalitis[16-18].

Patients with anti-NMDAR encephalitis may progress to autonomic instability, respiratory

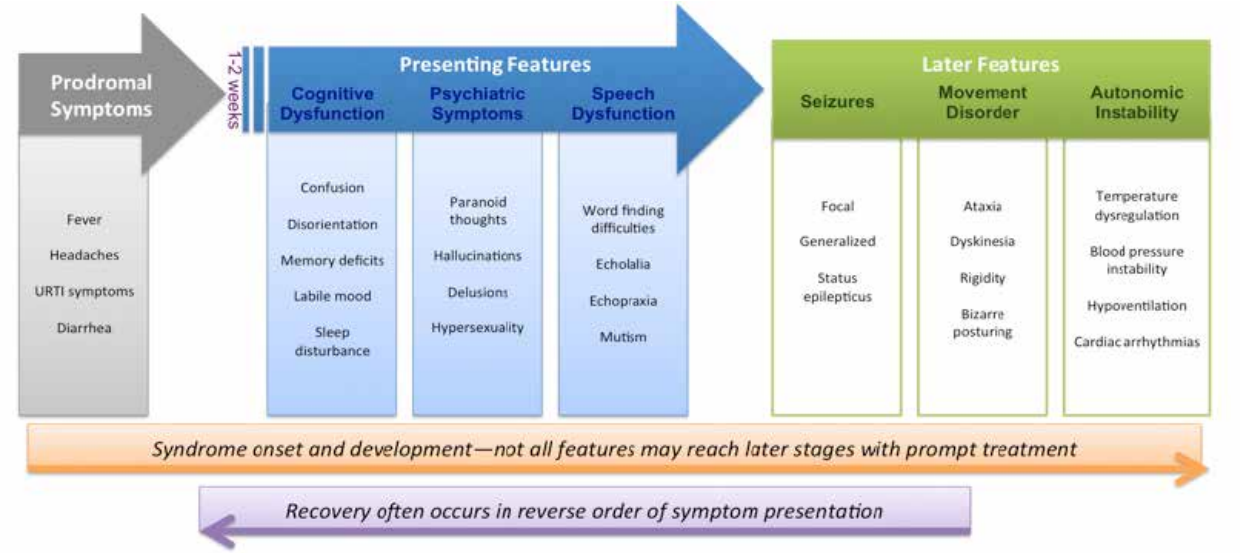

Fig 2: Typical acute clinical presentation of anti-NMDAR encephalitis in various stages of development.

distress, and death if left untreated[19]. Brain MRI scans of patients with anti-NMDAR encephalitis may be normal or may show increased T2 signals, especially in the medial temporal lobes. This pattern is similar to the findings seen in HSV encephalitis[16]. EEG is not specific for anti-NMDAR encephalitis, but it is useful for excluding subclinical seizures and for monitoring progress of the condition[20]. Up to half of anti-NMDAR encephalitis cases are associated with ovarian teratoma, so cancer screening is recommended[5,16]. Despite the compatibility of our patient's presentation with the most typical presentation, which is frequently documented in research for anti-NMDA receptor encephalitis (Figure 2)[14], her symptoms were not sufficient to establish anti-NMDAR encephalitis. Diagnosis requires a high clinical suspicion and is confirmed by the detection of immunoglobulin G antibodies in the GluN1 subunit of the NMDARs from serum or CSF[21]. Unfortunately, the patient's condition deteriorated quickly, and she died before more investigations could confirm the diagnosis.

A possible link has been reported between HSE and anti-NMDAR encephalitis, but no clear consensus exists regarding the causality, mechanism and management of the two conditions[4,7,22]. In 2012, Prüss *et al* identified anti-NMDAR antibodies in blood and CSF in 13 of 44 patients treated for HSE[23]. Similarly, Schein *et al* retrospectively identified anti-NMDAR immunoglobulin G in a CSF specimen of a 52-year-old woman diagnosed with HSE[22]. The results of a systematic review of the literature on PubMed between 1990 and 2017 revealed positive tests of anti-NMDAR encephalitis post-HSE in 11 published cases[22], but our review failed to find any reported cases of anti-NMDAR encephalitis post-HSE among bipolar patients. Overall, this points to the theory that HSE can be a trigger for anti-NMDAR encephalitis and that the treatment of these cases should include immunotherapies consisting of steroids, intravenous immunoglobulins and cyclophosphamide, as well as plasma exchange, if needed[22].

CONCLUSION

Patients with known psychiatric disorders who display any unusual presentation of psychiatric features in combination with cognitive impairments and neurological symptoms, including abnormal movements, should be viewed with particular concern. A high index of suspicion for an underlying etiology, with a broad approach to testing for infectious diseases and various neuronal autoantibodies, can prompt a correct diagnosis. Psychiatrists need to be familiar with the clinical presentations of both HSE and anti-NMDAR encephalitis. Furthermore, distinguishing between them is critically important, because the appropriate therapeutic approach differs for each. Our hope in presenting this case report is that it will help to increase awareness about the existence of co-morbid medical conditions in bipolar patients who show atypical clinical manifestations and treatment resistance to conventional therapies.

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REFERENCES

1. Kessing LV, Vradi E, McIntyre RS, Andersen PK. Causes of decreased life expectancy over the life span in bipolar disorder. J Affect Disord 2015; 180:142-147.
2. Marshe VS, Pira S, Mantere O, Bosche B, Looper KJ, Herrmann N, *et al*. C-reactive protein and cardiovascular risk in bipolar disorder patients: A systematic review. Prog Neuropsychopharmacol Biol Psychiatry 2017; 79(Pt B):442-451.
3. Kayser MS, Dalmau J. The emerging link between autoimmune disorders and neuropsychiatric disease. J Neuropsychiatry Clin Neurosci 2011; 23(1):90-97.
4. Venkatesan A, Benavides DR. Autoimmune encephalitis and its relation to infection. Curr Neurol Neurosci Rep 2015; 15(3):3.
5. Lancaster E. The diagnosis and treatment of autoimmune encephalitis. J Clin Neurol 2016; 12(1):1-13.
6. Sabah M, Mulcahy J, Zeman A. Herpes simplex encephalitis. BMJ 2012; 344:e3166.
7. Gnann Jr JW, Whitley RJ. Herpes simplex encephalitis: An update. Curr Infect Dis Rep 2017; 19(3):13.
8. Riancho J, Delgado-Alvarado M, Sedano MJ, Polo JM, Berciano J. Herpes simplex encephalitis: Clinical presentation, neurological sequelae and new prognostic factors. Ten years of experience. Neurol Sci 2013; 34(10):1879-1881.
9. McCabe K, Tyler K, Tanabe J. Diffusion-weighted MRI abnormalities as a clue to the diagnosis of herpes simplex encephalitis. Neurology 2003; 61(7):1015-1016.
10. Kim Y-S, Jung K-H, Lee S-T, Kang BS, Yeom JS, Moon J, *et al*. Prognostic value of initial standard EEG and MRI in patients with herpes simplex encephalitis. J Clin Neurol 2016; 12(2):224-229.
11. Lopez Roa P, Alonso R, de Egea V, Usubillaga R, Munoz P, Bouza E. PCR for Detection of herpes simplex virus in cerebrospinal fluid: Alternative acceptance criteria for diagnostic workup. J Clin Microbiol 2013; 51(9):2880-2883.
12. Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, *et al*. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. Lancet Neurol 2013; 12(2):157-165.
13. Carvalho F, Massano J, Coelho R. Neuropsychiatric symptoms in autoimmune encephalopathies : a clinician ' s guide. Int J Clin Neurosci Ment Heal 2014; 1:1-11.
14. Newman MP, Blum S, Wong RCW, Scott JG, Prain K, Wilson RJ, *et al*. Autoimmune encephalitis. Intern Med J 2016; 46(2):148-157.
15. Bost C, Pascual O, Honnorat J. Autoimmune encephalitis in psychiatric institutions: Current perspectives. Neuropsychiatr Dis Treat 2016; 12:2775-2787.
16. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011; 10(1):63-74.
17. Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: New developments and future challenges. Lancet Neurol 2011; 10(8):759-772.
18. Peery HE, Day GS, Dunn S, Fritzler MJ, Prüss H, De Souza C, *et al*. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun Rev 2012; 11(12):863-872.
19. Weaver M, Griffey RT. Anti-N-Methyl-d-Aspartate Receptor Encephalitis as an unusual cause of altered mental status in the Emergency Department. J Emerg Med 2016; 51(2):136-139.
20. Sutter R, Kaplan PW, Cervenka MC, Thakur KT, Asemota AO, Venkatesan A, *et al*. Electroencephalography for diagnosis and prognosis of acute encephalitis. Clin Neurophysiol 2015; 126(8):1524-1531.
21. Pruss H, Dalmau J, Harms L, Holtje M, Ahnert-Hilger G, Borowski K, *et al*. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010; 75(19):1735-1739.
22. Schein F, Gagneux-Brunon A, Antoine JC, Lavernhe S, Pillet S, Paul S, *et al*. Anti-N-methyl-d-aspartate receptor encephalitis after Herpes simplex virus-associated encephalitis: An emerging disease with diagnosis and therapeutic challenges. Infection 2017; 45(4):545-549.
23. Prüss H, Finke C, Höltje M, Hofmann J, Klingbeil C, Probst C, *et al*. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol 2012; 72(6):902-911.

Case Report

A typical involvement of Posterior Reversible Encephalopathy Syndrome diagnosed through brain magnetic resonance imaging

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ABSTRACT

We report the case of a patient who exhibited a sudden change in consciousness with seizure-like behavior. Brain magnetic resonance imaging (MRI) scans revealed confluent T2 hyperintensities in the white matter of the parieto-occipital cortex and subcortex and in parts of the frontal white matter. The T2 hyperintensities extended to the splenium of the corpus callosum as well as the bilateral cerebelli and brainstem, which are areas atypically involved in posterior reversible encephalopathy syndrome (PRES). The white matter of the parieto-occipital cortex and subcortex is the most frequently involved region per MRI scans. Per relevant literature, PRES prognosis is good and PRES-related brain lesions are reversible.

KEY WORDS: brain magnetic resonance imaging, parieto-occipital cortex, posterior reversible encephalopathy syndrome

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is characterized by seizures, headaches, changes in mental status, and visual disturbances; it is diagnosed through radiological methods. Although hypertension is a common presentation with PRES, it does not always accompany it. Brain magnetic resonance imaging (MRI) studies have shown that the white matter of the parieto-occipital cortex and subcortex is the most frequently involved region in PRES. Per relevant literature, PRES prognosis is good and the associated brain lesions are reversible[1].

CASE REPORT

A 39-year-old man was admitted to our emergency department with an episode of sudden change in consciousness and seizure-like behavior for 15 minutes. The patient had a history of hypertension without regular medical control. He exhibited unclear consciousness and agitated behavior on arrival to the emergency department. His Glasgow Coma Scale score was E4V4M5. His initial vital signs were as follows: body temperature, 36.1°C; heart rate, 136 beats per min; blood pressure, 238/174 mmHg; and oxygen saturation, 93% in room air without tachypnea. Oxygen was provided through a nasal cannula. Labetalol was administered repeatedly to control high blood pressure. A complete electrocardiogram revealed sinus tachycardia without ST segment and T wave changes. A chest X-ray revealed the absence of active lung lesions, pleural effusion, and borderline cardiomegaly. Laboratory data revealed leukocytosis without an elevated C-reactive protein level, acute kidney injury with a creatinine level of 1.5 mg/dL, metabolic acidosis, a lactate level of 23.9 mg/dL, hyperglycemia with a glucose level of 607 mg/dL, a high ammonia

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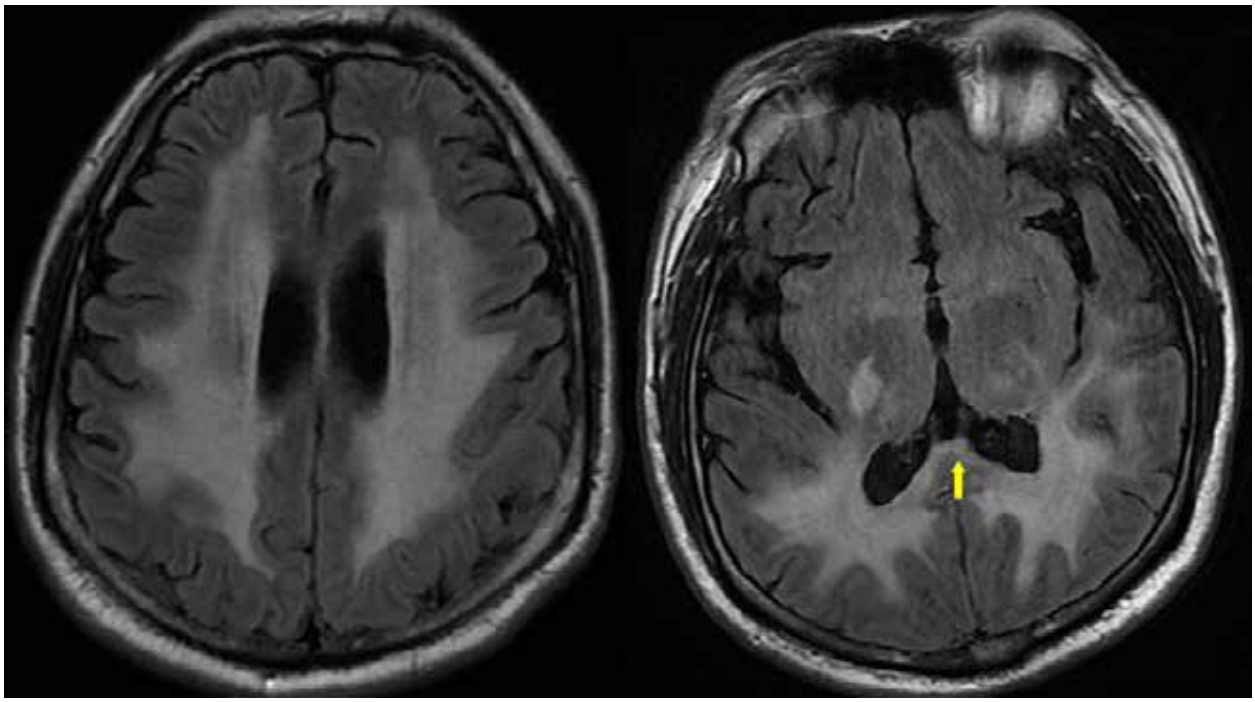

Fig 1: Multifocal confluent T2 hyperintensities involving the white matter in the bilateral cerebra (mainly in the occipito-parieto-temporal lobes and in some parts of the frontal lobes), splenium of the corpus callosum (yellow arrow), bilateral cerebelli, and brainstem.

level of 188 μg/dL, a mildly elevated troponin-T level of 0.027 ng/mL, normal liver function, and blood electrolyte levels within their normal range. Since the patient exhibited refractory hypertension (>200/100 mmHg), nicardipine was administered using a pump. Changes in the bilateral periventricular and subcortical white matter were visualized through computed tomography of the brain. A neurologist and psychiatrist were consulted. Acute epileptic disease was not the preferred diagnosis, and psychiatric disorders were relatively less likely. Brain MRI was arranged on a 1.5 T magnet in a supine position by using a circularly polarized head coil with field view of 23 cm and a slice thickness of 5 mm. Gadolinium (0.1 mmol/kg) was administered intravenously for the T1-weighted image examination. The pulse sequences were as follows: (1) T1 fluid-attenuated inversion recovery on the axial, coronal, and sagittal planes; (2) Turbo spin echo T2 weighted image and turbo flair (dark fluid) on the axial plane (Figure 1); (3) Echo-planar diffusion-weighted images (Figure 2); and (4) 3D time-of-flight magnetic resonance angiography. The images showed multifocal confluent T2 hyperintensities involving the cerebral white matter mainly in the bilateral occipito-parieto-temporal lobe sections of the bilateral frontal lobes, the splenium of the corpus callosum, the bilateral cerebelli, and the brainstem (Figure 1). The diffusion-weighted imaging did not reveal hyperintense restriction or a reduction in the apparent diffusion coefficient (Figure 2). PRES with atypical region involvement was suspected, and admission to the intensive care unit was arranged.

During admission to the intensive care unit, an endotracheal tube was inserted because the patient's Glasgow Coma Scale score had decreased to <8 with oxygen desaturation. Lumbar puncture results were negative. The results of tests for human immunodeficiency virus, varicella–zoster virus, cryptococcus, herpes simplex virus, tuberculosis, and syphilis were all negative. A drug profile of acetaminophen, amphetamine, barbiturate, cocaine, morphine, methadone, tricyclic antidepressant, and marijuana also showed negative results. Thyroid function and autoimmune profile data were all within the normal range. However, high vanillylmandelic acid levels in 24-hour urine (15.82 mg/24 hours) and high cortisol levels in blood (29.46 μg/dL) were observed. Therefore, computed tomography with contrast of chest and abdomen was performed; however, no evidence of pulmonary embolism, aortic dissection, or adrenal tumors was observed. Subsequently, a cardiologist was consulted, and an angiogram of the coronary and renal arteries was arranged. The report revealed no structural heart disease or arterial stenosis. The patient's consciousness improved, and he was extubated 12 days later. Hallucinations with depressive status and easy crying were noted after he regained consciousness. Oral medications were prescribed for hypertension. The patient was able to walk without

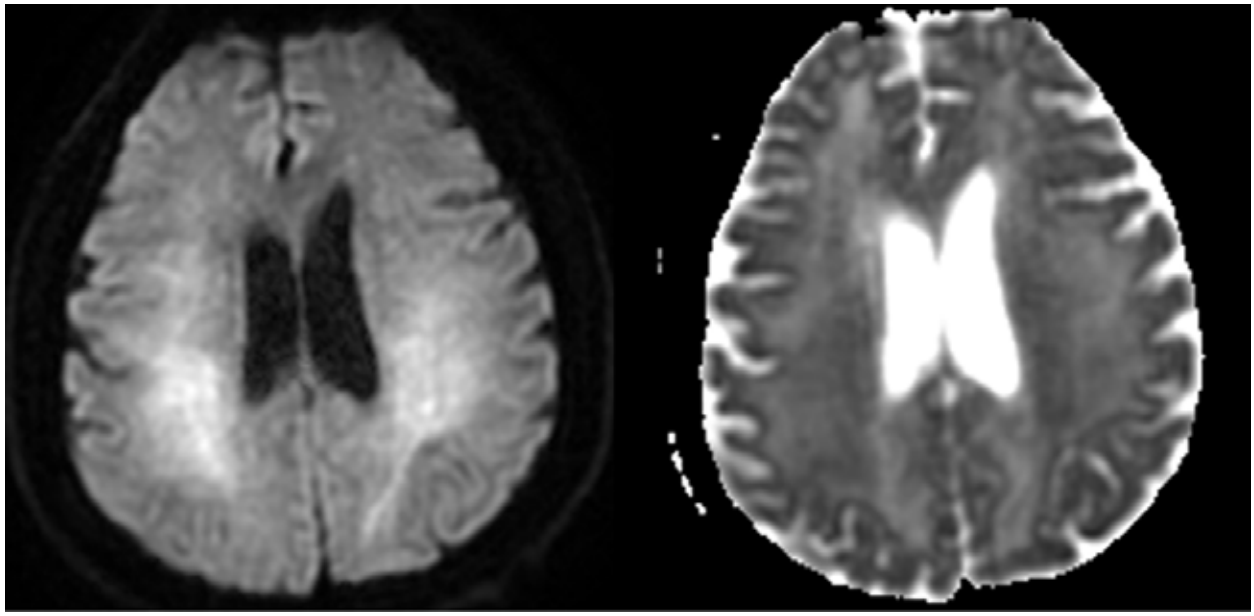

Fig 2: Diffusion-weighted imaging (left) and the apparent diffusion coefficient (right) of brain magnetic resonance imaging.

assistance, and his performance in activities of daily life gradually improved. Repeated brain MRI 21 days later did not reveal significant interval changes. We arranged another follow-up of brain MRI five months later. The findings suggested chronic hypertensive encephalopathy with a resolving acute hypertensive encephalopathy episode (Figure 3).

DISCUSSION

PRES is an emergency that results from the inability to respond to acute changes in blood pressure in the posterior circulation. Hyperperfusion that causes disruption of the blood-brain barrier results in vasogenic edema, and the most frequently involved area is the white matter of the parieto-occipital cortex

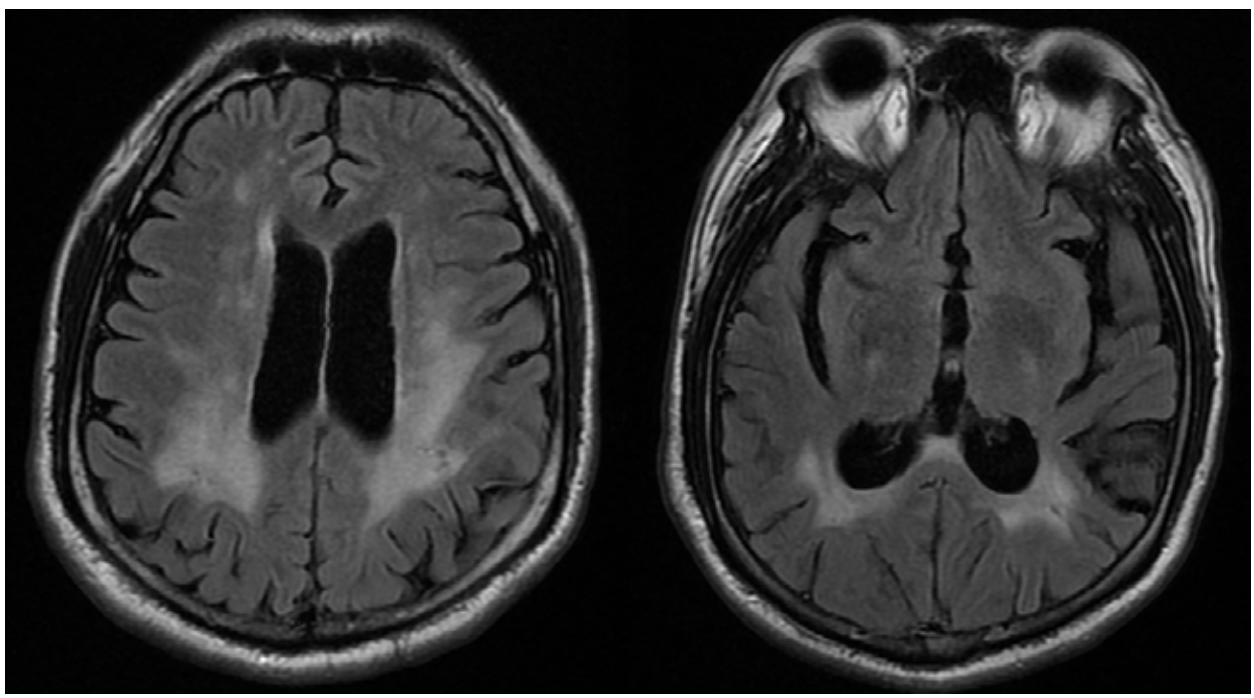

Fig 3: Brain magnetic resonance imaging five months later with findings suggesting chronic hypertensive encephalopathy with a resolving acute hypertensive encephalopathy episode

and subcortex. A relevant study demonstrated that MRI is a more sensitive technique than brain computed tomography for detecting initial atypical or subtle lesions in PRES[1]. One case series indicated that the posterior circulation of the brain has less sympathetic innervation than the anterior circulation, thus leading to a higher frequency of autoregulation loss[2]. However, several studies have shown that the involvement of the frontal lobe, basal ganglia, brain stem, deep white matter, and splenium is not uncommon[1,3]. Although a hemorrhage or an asymmetrical pattern presentation was not observed on the MRI scans of our patient, a pictorial review revealed that a diagnosis of PRES may not be precluded when the asymmetrical image patterns is detected[4].

Hypertension is frequently associated with PRES and may result from the failure of autoregulation to respond to a sudden increase in blood pressure and resultant blood-brain barrier disruption[3]. The blood pressure of our patient was high; the mean arterial pressure was 195 mmHg. He did not receive regular treatment for hypertension. Patients exhibit near normal blood pressure in up to 30% of the cases[5]. Additionally, a previous study demonstrated that atypical involvement is not strongly correlated with edema severity or blood pressure[6]. Additional studies are necessary to determine whether various mechanisms or manifestations cause the atypical involvement observed through imaging.

CONCLUSIONS

The actual mechanism of PRES is multifactorial. Various underlying diseases such as hypertension, infection, impaired kidney function, and autoimmunity may contribute to PRES development. Nonspecific presentation of this disease may cause difficulty in diagnosis, and PRES may not always be posterior and reversible. Atypical involvement in brain MRI is often encountered in PRES.

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Authors' contributions: HA Lin performed the literature search and composed the case report. CC Chao served as advisor and editor for this case report. Both authors have read and approved the final manuscript.

REFERENCES

1. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. Am J Neuroradiol 2007; 28(7):1320-1327.
2. Schwartz RB, Jones KM, Kalina P, Bajakian RL, Mantello MT, Garada B, *et al*. Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. Am J Roentgenol 1992; 159(2):379-383.
3. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, Teksam M. Posterior reversible encephalopathy syndrome: Incidence of atypical regions of involvement and imaging findings. Am J Roentgenol 2007; 189(4):904-912.
4. Stevens CJ, Heran MKS. The many faces of posterior reversible encephalopathy syndrome. Br J Radiol 2012; 85(1020):1566-1575.
5. Roth C, Ferbert A. The posterior reversible encephalopathy syndrome: What's certain, what's new? Pract Neurol 2011; 11(3):136-144.
6. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol 2015; 14(9):914-925.

Letter to Editor

Hyperbaric oxygen therapy for COVID-19: A potential choice for improving COVID-19-related hypoxemia

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Kuwait Medical Journal 2020; 52 (3): 326 - 327

Dear Editor,

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the pathogen that leads to the infection of the coronavirus disease 19 (COVID-19), is now becoming the origin of the unprecedented global public health crisis[1]. On March 11th 2020, the World Health Organization declared COVID-19 a pandemic, and it has now affected more than 120 countries on all continents[2].

With no sign of this pandemic reaching its peak, the shortage of intensive care unit (ICU) beds, ventilators and healthcare workers has now become a serious problem worldwide[3]. Since there are no drugs or specific therapeutics proving successful currently, respiratory support plays a key role in treating severe and critical cases of COVID-19. Hyperbaric oxygen therapy (HBOT), which has proved effective since the Spanish Flu Pandemic[4], is a non-invasive respiratory support method for relieving hypoxemia more effectively and comprehensively than normobaric oxygen therapy. We herein would like to propose that HBOT could be a potential solution to the global ventilator shortage or at least, reduce its possibility of application.

Respiratory support and advantage of HBOT

In most of the recent literature on COVID-19, the continuous development of intractable hypoxemia is an important manifestation of its progression. Approximately 17-29% of COVID-19 patients would develop into acute respiratory distress syndrome (ARDS)[5]. In such severe and critical cases, the Chinese Diagnosis and Treatment Protocol for COVID-19 (7th edition) recommended noninvasive mechanical ventilation or invasive mechanical ventilation[6]. However, the ICU mortality rate remains high, at 79% among those who required noninvasive ventilation, and 86% among those who required invasive mechanical ventilation[7].

Once intubated, the best way to improve oxygenation is to keep the patients in a prone position or provide extracorporeal membrane oxygenation. However, HBOT can improve oxygenation with a unique mechanism. Under the pressurization, more oxygen was able to dissolve in plasma, which means more free oxygen molecules were available in the circulation[8]. Thus, HBOT may be an option for avoiding invasive ventilation in critically-ill cases.

Latest research has revealed that the coronavirus attacks hemoglobin in the erythrocytes through a cascade cellular pathway, that ultimately jeopardizes the ability of hemoglobin in carrying oxygen[9]. In such conditions, HBOT may have specific advantages over the traditional ways of mechanical ventilation, because it independently increases the dissolved oxygen and can reach areas where erythrocytes may not be able to function[10]. Animals were able to thrive within the hyperbaric chamber even in the complete absence of erythrocytes[11]. Furthermore, other therapeutic effects of HBOT such as anti-infection and anti-inflammation also have practical clinical significance[12].

In China, the application of HBOT on COVID-19 cases have been implemented on a small-scale. One pilot report showed five severe cases that may be indicated for intubation were found free of hypoxic symptoms during HBOT, and significant clinical improvements within eight HBOT sessions[13]. The Huoshenshan Hospital, a COVID-19 designated makeshift hospital in Wuhan, has also witnessed a successful application of portable HBOT chambers on mild cases. Up to date, five clinical trials of HBOT for COVID-19 have been registered in the United States, which may potentially warrant the future application of HBOT on this global pandemic.

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Suggestions for HBOT on COVID-19

Before HBOT is ready for COVID-19, several important issues need to be considered. Firstly, the hyperbaric chamber can be used in hospitals specialized for infectious diseases such as Huoshenshan directly. However, when HBOT is to be used in general hospitals, the treatment surroundings need to be restructured into areas that are bio-safe and free of possible viral exposure, to meet the requirements of infection prevention and control. For instance, passages for patients and medical staff should be separated to avoid cross-infection. The hyperbaric chamber needs to be cleaned and disinfected between sessions with ultraviolet and chlorine-containing disinfectant. Since SARS-CoV-2 may spread as aerosol, the gas expired by patients during HBOT should be carefully sterilized before it is discharged.

Secondly, compared to severe cases, mild and moderate cases are more preferred for HBOT since these patients can switch oxygen mask and expectoration on their own, with no need for a medical attendant. In severe cases, the patients may be unable to manage themselves, and medical attendants who wear proper personal protection equipment are needed to prevent cross-infection.

Thirdly, the positions that a HBOT should hold in treating COVID-19 patients are included here:

1. To prevent light or mild patients from developing into severe or critical cases;
2. To be adjuvant therapy before invasive mechanical ventilation or reduce the chance of ventilation;
3. To provide respiratory protection before ventilator withdrawal;
4. To be compassionate therapy for critical ARDS patients;
5. For emergency use, when other kinds of oxygen therapy show no effect or ventilator shortage is unavoidable;
6. For patients with severe hypoxia, the session of HBOT or pressure and treatment time should be increased as well as staying cautious on possible oxygen intoxication.

In conclusion, HBOT is generally regarded as a safe therapy with few adverse events. While applied properly, HBOT may have utility in saving COVID-19 patients' lives by combating hypoxia. All kinds of monoplace and multiplace hyperbaric chambers can be chosen, if necessary, repurposing airplanes, railway tanks or gas tanker ships for use as medical pressure chambers. HBOT may be a promising solution for improving COVID-19-related hypoxemia, especially when ventilators are insufficient. The results of the two clinical trials are worth looking forward to. What is also worth noticing is that the effects of hyperbaric oxygen environments on the transmission dynamics of SARS-CoV-2, which warrants further research.

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Conflict of Interest: None

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REFERENCES

1. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, *et al*. COVID-19: towards controlling of a pandemic. Lancet 2020; 395(10229):1015-1018.
2. who.int [Internet]. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report [cited 2020 July 6]. Available from: https://www.who.int/.
3. The New York Times [Internet]. Kliff S, Satariano A, Silver-Greenberg J, Kulish N. There aren't enough ventilators to cope with the coronavirus. [cited 2020 Mar 8]. Available from: https://www.nytimes.com/.
4. Mehta V, De A, Balachandran C. Hyperbaric oxygen therapy. Journal of Pakistan Association of Dermatologists 2009; 19(3):164-167.
5. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for radiologists on COVID-19: An update—Radiology scientific expert panel. Radiology 2020; 296(2):E113-E114.
6. who.int [Internet]. National Health Protection Committee. [Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Seventh Edition)]. [cited 2020 Mar 12]. Available from: https://www.who.int/.
7. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine 2020; 8(5):475-481.
8. Geiderman JM, Ault MJ. Hyperbaric-oxygen therapy. N Engl J Med 1996; 335(22):1684.
9. Liu W, Li H. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. doi:10.26434%2Fchemrxiv.11938173.v8
10. Jain KK. Physical, Physiological, and Biochemical Aspects of Hyperbaric Oxygenation. In: Textbook of Hyperbaric Medicine. Springer, Cham. 2017.
11. Boerema I, Meyne NG, Brummelkamp WH, Bouma S, Mensch MH, Kamermans F, *et al*. [Life without blood]. Ned Tijdschr Geneeskd 1960; 104:949-954. Article in Dutch.
12. Thom SR. Hyperbaric oxygen–its mechanisms and efficacy. Plast Reconstr Surg 2011; 127(Suppl 1):131S-141S.
13. Zhong X, Tao X, Tang Y, Chen R. The outcomes of hyperbaric oxygen therapy to retrieve hypoxemia o f severe novel coronavirus pneumonia: first case report. Zhonghua Hanghai Yixue yu Gaoqiya Yixue Zazhi. 2020. doi: 10.3760/cma.j.issn.1009-6906.2020.0001

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2020; 52 (3) : 328 - 330

Implementation of Central Venous Catheter Bundle in an Intensive Care Unit in Kuwait: Effect on Central Line-Associated Bloodstream Infections

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J Infect Public Health. Jan-Feb 2016;9(1):34-41. doi: 10.1016/j.jiph.2015.05.001. Epub 2015 Jun 29.

Central line-associated bloodstream infection (CLABSIs) is an important healthcare-associated infection in the critical care units. It causes substantial morbidity, mortality and incurs high costs. The use of central venous line (CVL) insertion bundle has been shown to decrease the incidence of CLABSIs. Our aim was to study the impact of CVL insertion bundle on incidence of CLABSI and study the causative microbial agents in an intensive care unit in Kuwait. Surveillance for CLABSI was conducted by trained infection control team using National Health Safety Network (NHSN) case definitions and device days measurement methods. During the intervention period, nursing staff used central line care bundle consisting of (1) hand hygiene by inserter (2) maximal barrier precautions upon insertion by the physician inserting the catheter and sterile drape from head to toe to the patient (3) use of a 2% chlorohexidine gluconate (CHG) in 70% ethanol scrub for the insertion site (4) optimum catheter site selection. (5) Examination of the daily necessity of the central line. During the pre-intervention period, there were 5367 documented catheter-days and 80 CLABSIs, for an incidence density of 14.9 CLABSIs per 1000 catheter-days. After implementation of the interventions, there were 5052 catheter-days and 56 CLABSIs, for an incidence density of 11.08 per 1000 catheter-days. The reduction in the CLABSI/1000 catheter days was not statistically significant (P=0.0859). This study demonstrates that implementation of a central venous catheter post-insertion care bundle was associated with a reduction in CLABSI in an intensive care area setting.

Birth Prevalence of Orofacial Clefts in Kuwait From Hospital-Based Registration: Retrospective Study

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Cleft Palate Craniofac J. 2018 Nov;55(10):1450-1455. doi: 10.1177/1055665618766059. Epub 2018 Apr 30.

INTRODUCTION

Cleft lip and palate (CLAP) are the most common craniofacial anomalies and birth defects globally. Despite the fact that a tertiary care registry of clefts has existed in Kuwait since 2008, to date there is no published data regarding the prevalence of orofacial clefts in this population.

OBJECTIVE
To tabulate the pattern of orofacial clefts from tertiary care center registration during 2009 through 2014 and to estimate the prevalence and trend using population-based records.

METHODOLOGY
Data from all CLAP cases (born in Kuwait) registered in the central cleft center registry of the Al-Amiri hospital, Kuwait City, Kuwait, from January 2009 to December 2014 were obtained. Data regarding the type, severity, gender as well as nationality, parental consanguinity, and associated syndrome were obtained from medical records. Birth prevalence was tabulated against the population statistics for the period obtained from the central department of statistics.

RESULT
A total of 202 CLAP patients were recorded in the study period with a mean birth prevalence of 0.57 per 1000 live births (95% confidence interval [CI] .57 ± .23). The registry recorded 108 (53.2%) males and 94 (47.8%) females. Children born to Kuwaitis represented 53.7% of cases while those born to non-Kuwaitis represented 45.3%. The most common oral cleft was CLAP (47.3%), followed by cleft palate (30.5%), cleft lip (20.2%), and other facial clefts (2%). Other congenital anomalies were recognized in 33% of all cases. There were no statistically significant differences in oral cleft prevalence across gender or nationality.

CONCLUSION
The prevalence of oral cleft in Kuwait appears to be similar to those of other Middle Eastern populations.

Teenagers' Awareness of Peers' Substance and Drug Use in Kuwait

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J Addict Nurs. Apr/Jun 2017;28(2):55-62. doi: 10.1097/JAN.0000000000000166.

BACKGROUND
Teenage substance use is a global challenge, and youths residing in Kuwait are not immune from it. Tobacco products are licit; however, alcohol and other mood-altering illicit substance are prohibited with severe penalties including imprisonment. Youths residing in Kuwait are being initiated into the use of mood-altering substances like tobacco at an early age, and it is postulated that, as they grow older, they may progress into using alcohol and other prohibited illicit drugs.

AIMS
The aim of this study was to determine licit and illicit substance use by teenagers residing in Kuwait. The study will also explore their awareness of substance use among their peers.

DESIGN
A cross-sectional survey using a snowball sampling technique was used to recruit 190 teenagers aged 15-18 years residing in Kuwait. Data were collected using the 130-item questionnaire adapted from 1998 New Jersey Triennial Public High School Survey of Drug and Alcohol Use. Data collection was from September 2012 to June 2013.

DATA ANALYSIS
The Statistical Package for Social Sciences Version 22 for Windows was used. Pearson's chi-square, Kruskal-Wallis, and Mann-Whitney U tests were used to test the hypotheses.

RESULTS
Tobacco was the most commonly used substance by these teenagers; 8.4% were current smokers, and 50% had experimented. Age of initiation for 21% was before 14 years old. Hashish (marijuana) was the most commonly used illicit drug, with 3.7% current users and 5.3% claiming to have used it. More male than female teenagers in Grade 9 were using tobacco products ($\chi = 27.428$, $df = 5$, $p < .001$).

CONCLUSION
The use and abuse of mood/mind-altering licit and illicit substances appear to be increasing among older teenagers. Intensifying campaigns about the hazards of substance use and drug testing should start from the primary school level.

The Prevalence of Multiple Sclerosis Continues to Increase in Kuwait

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Mult Scler Relat Disord 2019 Jul;32:74-76. doi: 10.1016/j.msard.2019.04.033. Epub 2019 Apr 29.

BACKGROUND
The national MS registry was established in 2010 to assess the change in epidemiological status. The last reported data of the prevalence and incidence in Kuwait was in 2013.

OBJECTIVES
To update the prevalence and incidence rates of MS among Kuwaiti nationals.

METHODS
Using the national MS registry, a cross sectional study was conducted to estimate the number of all patients diagnosed with MS and clinically isolated syndrome suggestive of MS. The diagnosis was based on the revised 2017 McDonald criteria. The population census was acquired from the Public Authority of Civil Information.

RESULTS
On 30th June 2018, 1454 Kuwaiti MS patients fulfilled the diagnostic criteria. Women represented 66.8% of the analyzed cohort with female to male ratio of 2.01:1. The crude prevalence of MS was 104.88 (95% CI: 89.5-121.9) per 100,000 persons, which increased 1.6 times since 2013. Age-adjusted prevalence peaked in the 30-39 and 40-49 year age groups in both females and male, with a decreasing tendency beyond 50 years of age. The incidence of MS was 5.39 (95% CI: 4.3-6.8) per 100,000 persons. The 5-year incidence was 6.4 per 100,000, which has been stable since the last reported rate.

CONCLUSION
The prevalence of MS in Kuwaiti nationals continued to increase reflecting a better case ascertainment and improved awareness and referrals across the country. However, the incidence has stabilized in the last 5 years which was mostly driven by a slight decline in newly diagnosed cases in women compared to men despite the increase in the overall female to male ratio.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2020; 52 (3): 331 - 335

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United Arab Emirates / Dubai
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Academicsera – 753rd International Conference on **Sports Nutrition and Supplements** (ICSNS)
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International Conference on **Tissue Science and Regenerative Medicine**
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International Conference on **Cancer Research and Drug Development**
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Email: info@universal-conference.com

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Sep 08, 2020
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Email: cardiology@magnusmeetings.com

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Email: info.arsss@gmail.com

International Conference on **Tissue Science and Regenerative Medicine**
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Cyprus / Limassol
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Email: bloodcancer@europemeet.com

Scholars International Conference on **STD, HIV and AIDS Research**
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International Conference on **Tissue Science and Regenerative Medicine**
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Hypertension & CVD 2020
Oct 05, 2020
Austria / Vienna, Wien
Email: cardiology@euroconferences.net

819th International Conference on **Food Microbiology and Food Safety** (ICFMFS)
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United Arab Emirates / Dubai
Email: contact.wrfer@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Oct 15, 2020
Japan / Fukuoka
Email: contact.wrfer@gmail.com

World Conference on **Cancer Biology, Immuno Oncology and Drug Discovery**
Oct 19, 2020
United States of America / San Francisco, California
Email: Immuno-Oncology@eventqueries.com

New Trends in **Cancer Immunotherapy and Immunology**
Oct 19, 2020
Canada / Vancouver
E mail: cancer@longdomglobal.com

International Conference on **Tissue Science and Regenerative Medicine**
Oct 20, 2020
Syria / Aleppo
Email: info@eurasiaweb.com

International Conference on **Tissue Science and Regenerative Medicine**
Oct 20, 2020
Iraq / Baghdad
Email: info@eurasiaweb.com

World Conference on **Cancer Research and Drug Development**
Oct 21, 2020
Jordan / Zarqa
Email: info@worldresearchsociety.com

Annual Meeting on **Cancer Research**
Oct 26, 2020
United Arab Emirates / Dubai
Email: anajoy01c@gmail.com

International Conference on **Obesity, Weight Management and Nutrition Research** (ICOBWN)
Oct 26, 2020
India / Bengaluru, Karnataka
Email: info.irfsr@gmail.com

International Conference on **Oncolytic Virus Therapeutics** (ICOVT)
Oct 27, 2020
United States of America / New York
Email: info@conferenceonline.net

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Oct 29, 2020
Turkey / Istanbul
Email: contact.wrfer@gmail.com

International Virtual Conference on **Covid-19 and its Effect** (IVCCE)
Oct 29, 2020
Russian Federation / Moscow
Email: info@conferenceonline.net

International Conference on **Biological and Medical Sciences**
Nov 01, 2020
United Arab Emirates / Sharjah
Email: info.arsss@gmail.com

11th Global Conference on **Pharma Industry and Medical Devices**
Nov 03, 2020
United Kingdom / London
Email: info@igrnet.org

International Conference on **Medical, Medicine and Health Sciences** (ICMMH)
Nov 05, 2020
Turkey / Istanbul
Email: info@iierd.com

International Conference on **Biological** and **Medical Sciences**
Nov 08, 2020
United Kingdom / London
Email: info.arsss@gmail.com

3rd International Conference and Exhibition on **Public Health and Health Care Management**
Nov 09, 2020
Austria / Vienna
Email: olcphhm2020@gmail.com

International Conference on **Biological and Medical Sciences**
Nov 09, 2020
Qatar / Doha
Email: info.arsss@gmail.com

World Congress on **Medical Imaging and Clinical Research**
Egypt / Alexandria
Nov 11, 2020
Email: papers.scienceplus@gmail.com

World Congress on **Medical Imaging and Clinical Research**
Nov 14, 2020
United States of America / Austin
Email: papers.scienceplus@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Nov 17, 2020
United Kingdom / Cambridge
Email: contact.wrfer@gmail.com

Medical Summit and Expo on **Palliative Care, Women's health and Gynecology**
Nov 23, 2020
Italy / Rome
Email: conferencepalliativecare@gmail.com

945th International Conference on **Medical and Biosciences** (ICMBS)
Nov 28, 2020
Kuwait / Kuwait City
Email: info@researchworld.org

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Nov 28, 2020
Turkey / Istanbul
Email: contact.wrfer@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Nov 30, 2020
Indonesia / Jakarta
Email: contact.wrfer@gmail.com

965th International Conference on **Medical, Biological and Pharmaceutical Sciences** (ICMBPS)
Dec 01, 2020
Japan / Kyoto
Email: info@universal-conference.com

811th International Conference on **Pharma and Food** (ICPAF)
Dec 03, 2020
Germany / Munich
Email: info@academicsera.com

International Conference and Expo on **Drug Discovery, Designing and Development**
Jordan / Amman
Dec 05, 2020
Email: info@universal-conference.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 17, 2020
United Kingdom / Cambridge
Email: contact.wrfer@gmail.com

World Congress on **Medical and Health Informatics**
Scotland / Dundee
Dec 21, 2020
Email: info@conferencefora.org

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Spain / Barcelona
Dec 23, 2020
Email: contact.wrfer@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 25, 2020
United States of America / Athene
Email: contact.wrfer@gmail.com

International Conference on **Biological and Medical Sciences**
Italy / Milan
Dec 26, 2020
Email: info.arsss@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 28, 2020
Turkey / Istanbul
Email: contact.wrfer@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 30, 2020
Indonesia / Jakarta
Email: contact.wrfer@gmail.com

World Conference on **Cancer Research and Drug Development**
Jan 10, 2021
Syria / Damascus
Email: info@worldresearchsociety.com

World Conference on **Cancer Research and Drug Development**
Jan 21, 2021
Jordan / Zarqa
Email: info@worldresearchsociety.com

International Conference on **Medical and Health Sciences** (ICMHS)
Jan 28, 2021
Kuwait / Kuwait City
Email: info@iserd.co

WHO-Facts Sheet

1. Animal bites
2. Salmonella (non-typhoidal)
3. Sugars and dental caries
4. Tetanus
5. Vector-borne diseases

Compiled and edited by
Vineetha E Mammen

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1. ANIMAL BITES

KEY FACTS

- Antibiotic resistance is one of the biggest threats to global health, food security, and development today.
- Antibiotic resistance can affect anyone, of any age, in any country.
- Antibiotic resistance occurs naturally, but misuse of antibiotics in humans and animals is accelerating the process.
- A growing number of infections – such as pneumonia, tuberculosis, gonorrhoea, and salmonellosis – are becoming harder to treat as the antibiotics used to treat them become less effective.
- Antibiotic resistance leads to longer hospital stays, higher medical costs and increased mortality.

Introduction

Antibiotics are medicines used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use of these medicines.

Bacteria, not humans or animals, become antibiotic-resistant. These bacteria may infect humans and animals, and the infections they cause are harder to treat than those caused by non-resistant bacteria.

Antibiotic resistance leads to higher medical costs, prolonged hospital stays, and increased mortality.

The world urgently needs to change the way it prescribes and uses antibiotics. Even if new medicines are developed, without behaviour change, antibiotic resistance will remain a major threat. Behaviour changes must also include actions to reduce the spread of infections through vaccination, hand washing, practising safer sex, and good food hygiene.

Scope of the problem

Antibiotic resistance is rising to dangerously high levels in all parts of the world. New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases. A growing list of infections – such as pneumonia, tuberculosis, blood poisoning, gonorrhoea, and foodborne diseases – are becoming harder, and sometimes impossible, to treat as antibiotics become less effective.

Where antibiotics can be bought for human or animal use without a prescription, the emergence and spread of resistance is made worse. Similarly, in countries without standard treatment guidelines, antibiotics are often over-prescribed by health workers and veterinarians and over-used by the public.

Without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill.

Prevention and control

Antibiotic resistance is accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Steps can be taken at all levels of society to reduce the impact and limit the spread of resistance.

Individuals

To prevent and control the spread of antibiotic resistance, individuals can:

- Only use antibiotics when prescribed by a certified health professional.
- Never demand antibiotics if your health worker says you don't need them.
- Always follow your health worker's advice when using antibiotics.
- Never share or use leftover antibiotics.

Address correspondence to:
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- Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, practising safer sex, and keeping vaccinations up to date.
- Prepare food hygienically, following the WHO Five Keys to Safer Food (keep clean, separate raw and cooked, cook thoroughly, keep food at safe temperatures, use safe water and raw materials) and choose foods that have been produced without the use of antibiotics for growth promotion or disease prevention in healthy animals.

Policy makers

To prevent and control the spread of antibiotic resistance, policy makers can:

- Ensure a robust national action plan to tackle antibiotic resistance is in place.
- Improve surveillance of antibiotic-resistant infections.
- Strengthen policies, programmes, and implementation of infection prevention and control measures.
- Regulate and promote the appropriate use and disposal of quality medicines.
- Make information available on the impact of antibiotic resistance.

Health professionals

To prevent and control the spread of antibiotic resistance, health professionals can:

- Prevent infections by ensuring your hands, instruments, and environment are clean.
- Only prescribe and dispense antibiotics when they are needed, according to current guidelines.
- Report antibiotic-resistant infections to surveillance teams.
- Talk to your patients about how to take antibiotics correctly, antibiotic resistance and the dangers of misuse.
- Talk to your patients about preventing infections (for example, vaccination, hand washing, safer sex, and covering nose and mouth when sneezing).

Healthcare industry

To prevent and control the spread of antibiotic resistance, the health industry can:

- Invest in research and development of new antibiotics, vaccines, diagnostics and other tools.

Agriculture sector

To prevent and control the spread of antibiotic resistance, the agriculture sector can:

- Only give antibiotics to animals under veterinary supervision.
- Not use antibiotics for growth promotion or to prevent diseases in healthy animals.
- Vaccinate animals to reduce the need for antibiotics and use alternatives to antibiotics when available.
- Promote and apply good practices at all steps of production and processing of foods from animal and plant sources.
- Improve biosecurity on farms and prevent infections through improved hygiene and animal welfare.

Recent developments

While there are some new antibiotics in development, none of them are expected to be effective against the most dangerous forms of antibiotic-resistant bacteria.

Given the ease and frequency with which people now travel, antibiotic resistance is a global problem, requiring efforts from all nations and many sectors.

Impact

When infections can no longer be treated by first-line antibiotics, more expensive medicines must be used. A longer duration of illness and treatment, often in hospitals, increases health care costs as well as the economic burden on families and societies.

Antibiotic resistance is putting the achievements of modern medicine at risk. Organ transplantations, chemotherapy and surgeries such as caesarean sections become much more dangerous without effective antibiotics for the prevention and treatment of infections.

WHO response

Tackling antibiotic resistance is a high priority for WHO. A global action plan on antimicrobial resistance, including antibiotic resistance, was endorsed at the World Health Assembly in May 2015. The global action plan aims to ensure prevention and treatment of infectious diseases with safe and effective medicines.

The "Global action plan on antimicrobial resistance" has 5 strategic objectives:

- To improve awareness and understanding of antimicrobial resistance.
- To strengthen surveillance and research.
- To reduce the incidence of infection.
- To optimize the use of antimicrobial medicines.
- To ensure sustainable investment in countering antimicrobial resistance.

A political declaration endorsed by Heads of State at the United Nations General Assembly in New York in September 2016 signaled the world's commitment to taking a broad, coordinated approach to address the root causes of antimicrobial resistance across multiple sectors, especially human health, animal health and agriculture. WHO is supporting Member States to develop national action plans on antimicrobial resistance, based on the global action plan.

WHO has been leading multiple initiatives to address antimicrobial resistance:

World Antimicrobial Awareness Week

Held annually since 2015, WAAW is a global campaign that aims to increase awareness of antimicrobial resistance worldwide and to encourage best practices among the general public, health workers and policy makers to avoid the further emergence and spread of drug-resistant infections. Antimicrobials are critical tools in helping to fight diseases in humans, animals and plants. They include antibiotics, antivirals, antifungals and antiprotozoa. WAAW takes place every year from 18 to 24 November. The slogan has previously been, "Antibiotics: Handle with Care" but changed to "Antimicrobials: Handle with Care" in 2020 to reflect the broadening scope of drug resistant infections.

The Global Antimicrobial Resistance Surveillance System (GLASS)

The WHO-supported system supports a standardized approach to the collection, analysis and sharing of data related to antimicrobial resistance at a global level to inform decision-making, drive local, national and regional action.

Global Antibiotic Research and Development Partnership (GARDP)

A joint initiative of WHO and Drugs for Neglected Diseases initiative (DNDi), GARDP encourages research and development through public-private partnerships. By 2023, the partnership aims to develop and deliver up to four new treatments, through improvement of existing antibiotics and acceleration of the entry of new antibiotic drugs.

Interagency Coordination Group on Antimicrobial Resistance (IACG)

The United Nations Secretary-General has established IACG to improve coordination between international organizations and to ensure effective global action against this threat to health security. The IACG is co-chaired by the UN Deputy Secretary-General and the Director General of WHO and comprises high level representatives of relevant UN agencies, other international organizations, and individual experts across different sectors.

2. SALMONELLA (NON-TYPHOIDAL)

KEY FACTS

- *Salmonella* is 1 of 4 key global causes of diarrhoeal diseases.
- Most cases of salmonellosis are mild; however, sometimes it can be life-threatening. The severity of the disease depends on host factors and the serotype of *Salmonella*.
- Antimicrobial resistance is a global public health concern and *Salmonella* is one of the microorganisms in which some resistant serotypes have emerged, affecting the food chain.
- Basic food hygiene practices, such as "cook thoroughly", are recommended as a preventive measure against salmonellosis.

The burden of foodborne diseases is substantial: every year almost 1 in 10 people fall ill and 33 million of healthy life years are lost. Foodborne diseases can be severe, especially for young children. Diarrhoeal diseases are the most common illnesses resulting from unsafe food, 550 million people falling ill each year, including 220 million children under the age of 5 years. *Salmonella* is 1 of the 4 key global causes of diarrhoeal diseases.

Salmonella is a gram negative rods genus belonging to the Enterobacteriaceae family. Within 2 species, *Salmonella* bongori and Samonella enterica, over 2500 different serotypes or serovars have been identified to date. *Salmonella* is a ubiquitous and hardy bacteria that can survive several weeks in a dry environment and several months in water.

While all serotypes can cause disease in humans, a few are host-specific and can reside in only one or a few animal species: for example, *Salmonella* enterica serotype Dublin in cattle and *Salmonella* enterica serotype Choleraesuis in pigs. When these particular serotypes cause disease in humans, it is often invasive and can be life-threatening. Most serotypes, however, are present in a wide range of hosts. Typically, such serotypes cause gastroenteritis, which is often uncomplicated and does not need treatment, but disease can be severe in the young, the elderly, and patients with weakened immunity. This group features *Salmonella* enterica serotype Enteritidis and Salmonella enterica serotype Typhimurium, the two most important serotypes of Salmonella transmitted from animals to humans in most parts of the world.

The disease

Salmonellosis is a disease caused by the bacteria Salmonella. It is usually characterized by acute onset of fever, abdominal pain, diarrhoea, nausea and sometimes vomiting.

The onset of disease symptoms occurs 6–72 hours (usually 12–36 hours) after ingestion of Salmonella, and illness lasts 2–7 days.

Symptoms of salmonellosis are relatively mild and patients will make a recovery without specific treatment in most cases. However, in some cases, particularly in children and elderly patients, the associated dehydration can become severe and life-threatening.

Although large *Salmonella* outbreaks usually attract media attention, 60–80% of all salmonellosis cases are not recognized as part of a known outbreak and are classified as sporadic cases, or are not diagnosed as such at all.

Sources and transmission

- *Salmonella* bacteria are widely distributed in domestic and wild animals. They are prevalent in food animals such as poultry, pigs, and cattle; and in pets, including cats, dogs, birds, and reptiles such as turtles.
- *Salmonella* can pass through the entire food chain from animal feed, primary production, and all the way to households or food-service establishments and institutions.
- Salmonellosis in humans is generally contracted through the consumption of contaminated food of animal origin (mainly eggs, meat, poultry, and milk), although other foods, including green vegetables contaminated by manure, have been implicated in its transmission.
- Person-to-person transmission can also occur through the faecal-oral route.
- Human cases also occur where individuals have contact with infected animals, including pets. These infected animals often do not show signs of disease.

Treatment

Treatment in severe cases is electrolyte replacement (to provide electrolytes, such as sodium, potassium and chloride ions, lost through vomiting and diarrhoea) and rehydration.

Routine antimicrobial therapy is not recommended for mild or moderate cases in healthy individuals. This is because antimicrobials may not completely eliminate the bacteria and may select for resistant strains, which subsequently can lead to the drug becoming ineffective. However, health risk groups such as infants, the elderly, and immunocompromised patients may need to receive antimicrobial therapy. Antimicrobials are also administered if the infection spreads from the intestine to other body parts. Because of the global increase of antimicrobial resistance, treatment guidelines should be reviewed on a regular basis taking into account the resistance pattern of the bacteria based on the local surveillance system.

Prevention methods

Prevention requires control measures at all stages of the food chain, from agricultural production, to processing, manufacturing and preparation of foods in both commercial establishments and at home.

Preventive measures for *Salmonella* in the home are similar to those used against other foodborne bacterial diseases (see recommendations for food handlers below).

The contact between infants/young children and pet animals that may be carrying *Salmonella* (such as cats, dogs, and turtles) needs careful supervision.

National and regional surveillance systems on foodborne diseases are important means to know and follow the situation of these diseases and also to detect and respond to salmonellosis and other enteric infections in early stages, and thus to prevent them from further spreading.

Recommendations for the public and travellers

The following recommendations will help ensure safety while travelling:

- Ensure food is properly cooked and still hot when served.
- Avoid raw milk and products made from raw milk. Drink only pasteurized or boiled milk.
- Avoid ice unless it is made from safe water.
- When the safety of drinking water is questionable, boil it or if this is not possible, disinfect it with a reliable, slow-release disinfectant agent (usually available at pharmacies).
- Wash hands thoroughly and frequently using soap, in particular after contact with pets or farm animals, or after having been to the toilet.
- Wash fruits and vegetables carefully, particularly if they are eaten raw. If possible, vegetables and fruits should be peeled.

Recommendations for food handlers

WHO provides the following guidance for people handling food:

- Both professional and domestic food handlers should be vigilant while preparing food and should observe hygienic rules of food preparation.
- Professional food handlers who suffer from fever, diarrhoea, vomiting or visible infected skin lesions should report to their employer immediately.
- The WHO *Five keys to safer food* serve as the basis for educational programmes to train food handlers and educate consumers. They are especially important in preventing food poisoning. The five keys to Safer Food are:
  - keep clean
  - separate raw and cooked
  - cook thoroughly
  - keep food at safe temperatures
  - use safe water and raw materials.

Recommendations for producers of fruits, vegetables and fish

The WHO *Five keys to growing safer fruits and vegetables: promoting health by decreasing microbial contamination and the Five keys to safer aquaculture products to protect public health* provide rural workers, including small farmers who grow fresh fruits and

vegetables and fish for themselves, their families and for sale in local market with key practices to prevent microbial contamination.

The *Five keys to growing safer fruits and vegetables* **are:**

- Practice good personal hygiene.
- Protect fields from animal faecal contamination.
- Use treated faecal waste.
- Evaluate and manage risks from irrigation water.
- Keep harvest and storage equipment clean and dry.

The Five keys to safer aquaculture products to protect public health are:

- Practice good personal hygiene.
- Clean the pond site.
- Manage water quality.
- Keep fish healthy.
- Use clean harvest equipment and containers.

WHO response

In partnership with other stakeholders, WHO is strongly advocating the importance of food safety as an essential element in ensuring access to safe and nutritious diets. WHO is providing policies and recommendations that cover the entire food chain from production to consumption, making use of different types of expertise across different sectors.

WHO is working towards the strengthening of food safety systems in an increasingly globalized world. Setting international food safety standards, enhancing disease surveillance, educating consumers and training food handlers in safe food handling are amongst the most critical interventions in the prevention of foodborne illnesses.

3. SUGARS AND DENTAL CARIES

KEY FACTS

- Dental caries (also known as tooth decay or dental cavities) is the most common noncommunicable disease worldwide.
- Severe dental caries affects general health and often causes pain and infection, which may result in tooth extraction.
- Dental caries is an expensive disease to treat, consuming 5–10% of healthcare budgets in industrialized countries, and is among the main reasons for hospitalization of children in some high-income countries.
- Free sugars are the essential dietary factor in the development of dental caries. Dental caries develops when bacteria in the mouth metabolize sugars to produce acid that demineralizes the hard tissues of the teeth (enamel and dentine).
- In many countries, sugars-sweetened beverages, including fruit-based and milk-based sweetened drinks and 100% fruit juices, are a primary source of free sugars, as well as confectionery, cakes, biscuits, sweetened cereals, sweet desserts, sucrose, honey, syrups and preserves.
- Limiting free sugars intake to less than 10% of total energy intake – and ideally even further, to less than 5% – minimizes the risk of dental caries throughout the lifecourse.
- Severe dental caries is a frequent cause of absenteeism at school or work. An association between dental caries and undernutrition in children has been reported in some low- and middle-income countries; however, whether this is cause or effect, or both, remains to be determined.

Dental caries is a major public health problem globally and is the most widespread noncommunicable disease (NCD). It is also the most prevalent condition included in the 2015 Global Burden of Disease Study, ranking first for decay of permanent teeth (2.3 billion people) and 12th for deciduous teeth (560 million children).

Dental caries can be prevented by avoiding dietary free sugars. Moreover, dental caries is largely preventable through simple and cost-effective population-wide and individual interventions, whereas treatment is costly, and is often unavailable in low- and middle-income countries.

Teeth affected by caries are often extracted (pulled out) when they cause pain or discomfort.

Severe dental caries can impair quality of life, including difficulties in eating and sleeping, and in its advanced stages (abscesses), it may result in pain and chronic systemic infection or adverse growth patterns. Tooth decay is a frequent cause of absence from school or work.

Risk factors

Everyone is at risk of dental caries, but children and adolescents are most at risk. Almost half of the world's population is affected by dental caries, making it the most prevalent of all health conditions. High levels of dental caries occur in middle-income countries, where sugars consumption is high. The majority of dental caries occurs in adults because the disease is cumulative. There is a clear dose-response relationship between sugars consumption and dental caries. The disease is also associated with socioeconomic status, with high prevalence rates among the poor and disadvantaged population groups.

Dental caries develops over time; loss of tooth substance (enamel and dentine) is caused by acid production resulting from bacterial metabolism of sugars. Early stages are often without symptoms, but advanced stages of dental caries may lead to pain, infections and abscesses, or even sepsis.

It has been estimated that, globally in 2010, US$ 298 billion was spent on direct costs associated with dental caries. In addition, indirect costs came to US$ 144 billion, with the total financial cost reaching US$ 442 billion in 2010.

Prevention and control

Population-wide strategies to reduce free sugars consumption are the key public health approach that should be a high and urgent priority. Because dental caries is the result of lifelong exposure to a dietary risk factor (i.e. free sugars), even a small reduction in the risk of dental caries in childhood is of significance in later life; therefore, to minimize the lifelong risk of dental caries, free sugars intake should be as low as possible.

It is important that population-wide prevention interventions are universally available and accessible. Such interventions include the use of fluoride and comprehensive patient-centred essential oral health care.

Challenges

Dental caries disproportionally affect poor and disadvantaged populations, which have lower access to prevention and care. Often, dental caries does not receive adequate priority in health planning due to an underestimation of the true burden and impact of the disease. The focus of interventions is generally characterized by an isolated disease approach and a focus on costly clinical treatment, rather than on integrated cost-effective public health strategies that address entire populations and focus on common risk factors for NCDs.

Economic growth is associated with increased access to sugar-sweetened beverages and other dietary sources of free sugars. Increased availability of sugars in the absence of adequate oral health preventive measures is associated with a marked increase in the burden of oral disease.

WHO response

WHO works with Member States and partners on policies and programs to reduce dental caries as part of work to prevent noncommunicable diseases. Key policies include:

- taxation of sugar-sweetened beverages and foods with high free sugar content;
- implementing clear nutrition labelling, including the information on sugars contained in a product;
- regulating all forms of marketing and advertising of food and beverages high in free sugars to children;
- improving the food environment in public institutions, particularly schools, through regulating sales of foods and beverages high in free sugars; and
- prioritizing awareness and access to clean water as a drink that is 'safe for teeth'.

Implementation of public health strategies to promote the use of fluoride should also be encouraged, although it does not completely prevent dental caries if implemented as a sole (i.e. an isolated) action. Addressing the cause (i.e. free sugars) is therefore essential in preventing and reducing dental caries.

[1] The severity of dental caries may be measured by using indices such as the DMFT/dmft index (where upper case denotes permanent dentition and lower case primary dentition), which records the number of decayed (D), missing (M) and filled (F) teeth.

[2] Free sugars include all monosaccharides and disaccharides added to foods and drinks by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates (WHO Guideline on sugars intake for adults and children: https://www.who.int/publications-detail/9789241549028/).

4. TETANUS

KEY FACTS

- Tetanus is acquired through infection of a cut or wound with the spores of the bacterium Clostridium tetani, and most cases occur within 14 days of infection. Tetanus cannot be transmitted from person to person.
- Tetanus can be prevented through immunization with tetanus-toxoid-containing vaccines (TTCV). However, people who recover from tetanus do not have natural immunity and can be infected again.
- The majority of reported tetanus cases are birth-associated among newborn babies and mothers who have not been sufficiently vaccinated with TTCV.
- In 2015, about 34 000 newborns died from neonatal tetanus, a 96% reduction since 1988, largely due to scaled-up immunization with TTCV.
- In 2016, 86% of infants worldwide were vaccinated with 3 doses of diphtheria-tetanus-pertussis (DTP) containing vaccine.

Tetanus is an acute infectious disease caused by spores of the bacterium Clostridium tetani. The spores are found everywhere in the environment, particularly in soil, ash, intestinal tracts/feces of animals and humans, and on the surfaces of skin and rusty tools like nails, needles, barbed wire, etc. Being very resistant to heat and most antiseptics, the spores can survive for years.

Anyone can get tetanus, but the disease is particularly common and serious in newborn babies and pregnant women who have not been sufficiently immunized with tetanus-toxoid-containing vaccines. Tetanus during pregnancy or within 6 weeks of the end of pregnancy is called "maternal tetanus", and tetanus within the first 28 days of life is called "neonatal tetanus".

The disease remains an important public health problem in many parts of the world, but especially in low-income countries or districts, where immunization coverage is low, and unclean birth practices are common. Neonatal tetanus occurs when nonsterile instruments are used to cut the umbilical cord or when contaminated material is used to cover the umbilical stump. Deliveries carried out by people with unclean hands or on a contaminated surface are also risk factors.

In 2015, approximately 34 000 newborns died from neonatal tetanus, a 96% reduction from 1988 when an estimated 787 000 newborn babies died of tetanus within their first month of life. However, there is increased risk of tetanus in adolescent and adult males who undergo circumcision due to waning immunity and limited opportunity for receiving booster doses in males in many countries.

Symptoms and Diagnosis

The incubation period of tetanus varies between 3 to 21 days after infection. Most cases occur within 14 days.

Symptoms can include:

- jaw cramping or the inability to open the mouth
- muscle spasms often in the back, abdomen and extremities
- sudden painful muscle spasms often triggered by sudden noises
- trouble swallowing
- seizures
- headache
- fever and sweating
- changes in blood pressure or fast heart rate.

In neonatal tetanus, symptoms include muscle spasms, which are often preceded by the newborn's inability to suck or breastfeed, and excessive crying.

Tetanus is diagnosed on the basis of clinical features and does not require laboratory confirmation. The WHO definition of a confirmed neonatal tetanus case is an illness occurring in an infant who has the normal ability to suck and cry in the first 2 days of life, but who loses this ability between days 3 and 28 of life and becomes rigid or has spasms.

The WHO definition of non-neonatal tetanus requires at least one of the following signs: a sustained spasm of the facial muscles in which the person appears to be grinning, or painful muscular contractions. Although this definition requires a history of injury or wound, tetanus may also occur in patients who are unable to recall a specific wound or injury.

Treatment

Tetanus is a medical emergency requiring:

- care in the hospital
- immediate treatment with medicine called human tetanus immune globulin (TIG)
- aggressive wound care
- drugs to control muscle spasms
- antibiotics
- tetanus vaccination.

People who recover from tetanus do not have natural immunity and can be infected again, and therefore need to be immunized.

Prevention

Tetanus can be prevented through immunization with tetanus-toxoid-containing vaccines (TTCV), which are included in routine immunization programmes globally and administered during antenatal care contacts.

To be protected throughout life, WHO recommends that an individual receives 6 doses (3 primary plus 3 booster doses) of TTCV. The 3-dose primary series should begin as early as 6 weeks of age, with subsequent doses given with a minimum interval of 4 weeks between doses. The 3 booster doses should preferably be given during the second year of life (12–23 months), at 4–7 years of age, and at 9–15 years of age. Ideally, there should be at least 4 years between booster doses.

There are many kinds of vaccines used to protect against tetanus, all of which are combined with vaccines for other diseases:

- Diphtheria and tetanus (DT) vaccines
- Diphtheria, tetanus, and pertussis (whooping cough) (DTaP) vaccines
- Tetanus and diphtheria (Td) vaccines
- Tetanus, diphtheria, and pertussis (Tdap) vaccines

Neonatal tetanus can be prevented by immunizing women of reproductive age with TTCV, either during pregnancy or outside of pregnancy. Additionally, robust medical practices can also prevent tetanus disease including clean delivery and cord care during childbirth, and proper wound care for surgical and dental procedures.

In countries where national programmes have maintained high immunization coverage for several decades, tetanus incidence rates are very low.

WHO Response

The global neonatal tetanus elimination goal was launched at the World Health Assembly in 1989 to reduce neonatal tetanus as a public health problem (defined as less than one case of neonatal tetanus per 1000 live births in every district) in all countries.

The Maternal and Neonatal Tetanus Elimination (MNTE) Initiative was launched by UNICEF, WHO and the United Nations Population Fund (UNFPA) in 1999, revitalizing the goal of MNTE as a public health problem.

As of April 2018, there are 14 countries that have not achieved MNTE.

Once MNTE has been achieved, maintaining elimination will require continued strengthening of routine immunization activities for both pregnant women and children, maintaining and increasing access to clean deliveries, reliable neonatal tetanus surveillance, and introduction and/or strengthening of school-based immunization, where feasible.

To sustain MNTE and protect all persons from tetanus, WHO recommends that 6 doses of tetanus-containing vaccine be given to all persons from childhood to adolescence.

5. VECTOR-BORNE DISEASES

KEY FACTS

- Vector-borne diseases account for more than 17% of all infectious diseases, causing more than 700 000 deaths annually. They can be caused by either parasites, bacteria or viruses.
- Malaria is a parasitic infection transmitted by Anopheline mosquitoes. It causes an estimated 219 million cases globally, and results in more than 400,000 deaths every year. Most of the deaths occur in children under the age of 5 years.
- Dengue is the most prevalent viral infection transmitted by Aedes mosquitoes. More than 3.9 billion people in over 129 countries are at risk of contracting dengue, with an estimated 96 million symptomatic cases and an estimated 40,000 deaths every year.
- Other viral diseases transmitted by vectors include chikungunya fever, Zika virus fever, yellow fever, West Nile fever, Japanese encephalitis (all transmitted by mosquitoes), tick-borne encephalitis (transmitted by ticks).
- Other vector-borne diseases such as Chagas disease (transmitted by triatomine bugs), leishmaniasis (sandflies) and schistosomiasis (snails) affect hundreds of millions of people worldwide.
- Many of vector-borne diseases are preventable, through protective measures, and community mobilisation.

Vectors

Vectors are living organisms that can transmit infectious pathogens between humans, or from animals to humans. Many of these vectors are bloodsucking insects, which ingest disease-producing microorganisms during a blood meal from an infected host (human or animal) and later transmit it into a new host, after the pathogen has replicated. Often, once a vector becomes infectious, they are capable of transmitting the pathogen for the rest of their life during each subsequent bite/blood meal.

Vector-borne diseases

Vector-borne diseases are human illnesses caused by parasites, viruses and bacteria that are transmitted by vectors. Every year there are more than 700,000 deaths from diseases such as malaria, dengue, schistosomiasis, human African trypanosomiasis, leishmaniasis, Chagas disease, yellow fever, Japanese encephalitis and onchocerciasis.

The burden of these diseases is highest in tropical and subtropical areas, and they disproportionately affect the poorest populations. Since 2014, major outbreaks of dengue, malaria, chikungunya, yellow fever and Zika have afflicted populations, claimed lives, and overwhelmed health systems in many countries. Other diseases such as Chikungunya, leishmaniasis and lymphatic filariasis cause chronic suffering, life-long morbidity, disability and occasional stigmatisation.

Distribution of vector-borne diseases is determined by a complex set of demographic, environmental and social factors. Global travel and trade, unplanned urbanization, and en

List of vector-borne diseases, according to their vector

The following table is a non-exhaustive list of vector-borne disease, ordered according to the vector by which it is transmitted. The list also illustrates the type of pathogen that causes the disease in humans.

WHO response

The **"***Global Vector Control Response (GVCR) 2017–2030"* was approved by the World Health Assembly in 2017. It provides strategic guidance to countries and development partners for urgent strengthening of vector control as a fundamental approach to preventing disease and responding to outbreaks. To achieve this a re-alignment of vector control programmes is required, supported by

Vector	Disease caused	Type of pathogen
Mosquito		
Aedes	Chikungunya	Virus
	Dengue	Virus
	Lymphatic filariasis	Parasite
	Rift Valley fever	Virus
	Yellow Fever	Virus
	Zika	Virus
Anopheles	Lymphatic filariasis	Parasite
	Malaria	Parasite
Culex	Japanese encephalitis	Virus
	Lymphatic filariasis	Parasite
	West Nile fever	Virus
Aquatic snails	Schistosomiasis (bilharziasis)	Parasite
Blackflies	Onchoceriasis (river blindness)	Parasite
Fleas	Plague (transmitted from rats to humans)	Bacteria
	Tungiasis	Ecto parasite
Lice	Typhus	Bacteria
	Louse-borne relapsing fever	Bacteria
Sandflies	Leishmaniasis	Bacteria
	Sandfly fever (phlebotomus fever)	Virus
Ticks	Crimean-Congo haemorrhagic fever	Virus
	Lyme disease	Bacteria
	Relapsing fever (borreliosis)	Bacteria
	Rickettsial diseases (eg: spotted fever and Q fever)	Bacteria
	Tick-borne encephalitis	Virus
	Tularaemia	Bacteria
Triatome bugs	Chagas disease (American trypanosomiasis)	Parasite
Tsetse flies	Sleeping sickness (African trypanosomiasis)	Parasite

increased technical capacity, improved infrastructure, strengthened monitoring and surveillance systems, and greater community mobilization. Ultimately, this will support implementation of a comprehensive approach to vector control that will enable the achievement of disease-specific national and global goals and contribute to achievement of the Sustainable Development Goals and Universal Health Coverage.

WHO Secretariat provides strategic, normative and technical guidance to countries and development partners for strengthening vector control as a fundamental approach based on GVCR to preventing disease and responding to outbreaks. Specifically WHO responds to vector-borne diseases by:

- providing evidence-based guidance for controlling vectors and protecting people against infection;
- providing technical support to countries so that they can effectively manage cases and outbreaks;
- supporting countries to improve their reporting systems and capture the true burden of the disease;
- providing training (capacity building) on clinical management, diagnosis and vector control with support from some of its collaborating centres; and
- supporting the development and evaluation of new tools, technologies and approaches for vector-borne diseases, including vector control and disease management technologies.

A crucial element in reducing the burden of vector-borne diseases is behavioural change. WHO works with partners to provide education and improve public awareness, so that people know how to protect themselves and their communities from mosquitoes, ticks, bugs, flies and other vectors.

Access to water and sanitation is a very important factor in disease control and elimination. WHO works together with many different government sectors to improve water storage, sanitation, thereby helping to control these diseases at the community level.