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Results of a Real-life Study of Entecavir in Patients with Chronic Hepatitis B (2007-2014): A Study from Turkey

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2Department of Clinical Microbiology and Infectious Diseases, Eskisehir Yunus Emre State Hospital, Eskisehir, Turkey
3Department of Clinical Microbiology and Infectious Diseases, Kocaeli State Hospital, Kocaeli, Turkey

ABSTRACT

Objectives: Evaluate real-life data to determine long-term treatment efficacy and safety of entecavir (ETV) in patients with chronic hepatitis B (CHB)

Design: Retrospective study

Setting: Department of Clinical Microbiology and Infectious Diseases, Eskisehir Yunus Emre State Hospital, Eskisehir, Turkey

Subjects: Thirty-nine nucleos(t)ide analog (NA)-naive and NA-experienced patients who were treated for CHB between April 2007 and May 2014

Interventions: Oral ETV at a dose of 0.5 mg/day in NA-naive patients and 1 mg/day in NA-experienced patients.

Main outcome measures: Virological response, virological breakthrough and alanine aminotransferase (ALT) normalization rates and ETV-associated adverse effects were determined.

Results: Virological response rates at 1, 2, 3, 4, 5 and 6 years after initiating ETV treatment were 69.2%, 82.9%, 85.3%, 96.6%, 100% and 100%, respectively. ALT normalization rates at 1, 2, 3, 4, 5 and 6 years after treatment initiation were 76.9%, 85.7%, 88.2%, 89.7%, 92.3% and 92.8%, respectively. Cumulative rate of virological breakthrough at the end of year 6 was 9% and 35.2% in NA-naive and NA-experienced patients, respectively. No patient discontinued ETV treatment due to adverse effects.

Conclusions: Efficient viral suppression with long-term ETV treatment was achieved in NA-naive patients after six years.

INTRODUCTION

Chronic hepatitis B (CHB) affects more than 350 million people globally and leads to more than 500,000 deaths annually, primarily due to long-term complications such as cirrhosis and hepatocellular carcinoma (HCC)[1,2]. Therefore, the primary goal of therapy in patients with CHB is prevention of progression to cirrhosis and HCC via suppression of viral replication[3-5]. Recommended drugs in current guidelines for CHB treatment include interferon, pegylated interferon, nucleoside analogs [lamivudine (LAM), telbivudine, and entecavir (ETV)], and nucleotide analogs [adefovir dipivoxil (ADV), and tenofovir dipivoxil fumarate][6].

Nucleos(t)ide analogs (NAs) target hepatitis B virus (HBV) reverse transcriptase activity and are potent inhibitors of viral replication[7]. ETV, a deoxyguanosine analog that suppresses viral replication by potent inhibition of HBV DNA polymerase[8,9] has been in use since 2007 in Turkey. A previous study showed that the viral resistance and virological response rates in NA-naive patients were 1.2% and 93%, respectively, after five years of ETV monotherapy. However, the genotypic resistance rate of ETV was 51% in LAM-refractory patients at the end of five years, and the virological breakthrough rate was 43%[10]. Thus, assessment of ETV efficiency in NA-experienced patients is critical, as treatment failure has been increasingly observed in patients receiving different NAs[11]. We, therefore, evaluated real-life data to determine long-term efficacy and safety of ETV in patients with CHB at a single, tertiary care hospital in Turkey.

SUBJECTS AND METHODS

In this study, the outpatient clinical medical records of 39 patients with a diagnosis of CHB [hepatitis B surface (HBs) antigen (HBsAg) positivity for > 6 months] who were treated with ETV between April
2007 and May 2014 were retrospectively evaluated. The cohort included both NA-naive and NA-experienced patients. The study was approved by the ethics committee of Eskisehir Yunus Emre State Hospital.

ETV treatment was initiated in patients meeting the following criteria: Alanine aminotransferase (ALT) more than twice the upper limit of normal and HBV DNA ≥ 20,000 IU/mL in hepatitis B envelope (HBe) antigen (HBeAg)-positive patients, ALT more than twice the upper limit of normal and HBV DNA ≥ 2,000 IU/mL in HBeAg-negative patients, and presence of moderate-to-severe histological injury at concomitant liver biopsy.

ETV was administered orally at a dose of 0.5 mg/day in NA-naive patients and 1 mg/day in LAM-experienced patients. Patients with a history of alcohol consumption, hepatitis C, hepatitis D, and/or human immunodeficiency virus (HIV) coinfection, HCC, decompensated cirrhosis, and autoimmune diseases were excluded from the study.

Physical examination, complete blood cell counts and biochemical tests that included ALT, aspartate aminotransferase, gamma glutamyl transferase, albumin, bilirubin and creatinine were performed on all patients before initiating ETV treatment. Patients were re-evaluated every three months at an outpatient clinic; complete blood cell counts, biochemical tests and measurement of HBV DNA level were performed every three months. Viral markers, i.e., HBsAg, HBeAg and anti-HBs and anti-HBc antibodies were measured before the start of ETV treatment and every 6 - 12 months thereafter.

In addition, patients were screened for HCC with abdominal ultrasonography and serum alpha-fetoprotein levels. Biopsy was performed on all patients with no contraindications for liver biopsy. Fibrosis and histological activity index were scored according to the Knodell scoring system modified by Ishak, and biochemical tests that included ALT, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, albumin, bilirubin and creatinine were performed every three months at an outpatient clinic; complete blood cell counts, biochemical tests and measurement of HBV DNA level were performed every three months. Viral markers, i.e., HBsAg, HBeAg and anti-HBs and anti-HBc antibodies were measured before the start of ETV treatment and every 6 - 12 months thereafter. In addition, patients were screened for HCC with abdominal ultrasonography and serum alpha-fetoprotein levels. Biopsy was performed on all patients with no contraindications for liver biopsy. Fibrosis and histological activity index were scored according to the Knodell scoring system modified by Ishak.

HBsAg, anti-HBs, HBeAg, anti-HBe, hepatitis B core antibody, antibody to hepatitis D, antibody to hepatitis C and antibody to human immune deficiency virus were measured by enzyme-linked immunosassays on the Liaison® (DiaSorin, Saluggia, Italy). HBV DNA was measured by the following real-time polymerase chain reaction (RT-PCR) assays: the Cobas® Taqman RT-PCR with a lower detection limit of 6 IU/mL between 2007 and 2009, Rotorgene® Q RT-PCR with a lower detection limit of 20 IU/mL between 2010 and 2011, Qiagen® artus PCR with a lower detection limit of 11 IU/mL between 2012 and 2014, and Rotorgene® 6000 RT-PCR with a lower detection limit of 3.8 IU/mL in 2014.

The main outcome measure was the rate of virological response, and the secondary measures were loss of HBeAg and HbsAg, HBeAg seroconversion, ALT normalization, and frequency and cause of virological breakthrough during ETV treatment. Reduction of serum HBV DNA to below the level of detection, i.e., < 400 copies/ml, by PCR every year after ETV treatment initiation was defined as virological response. HBeAg seroconversion was defined as loss of HBeAg and appearance of anti-HBe antibody in HBeAg-positive patients[46]. Virological breakthrough was defined as an increase in serum HBV DNA level > 1 log10 copies/mL above nadir during treatment.

Descriptive data were expressed as means ± standard deviation, median, number, and percent frequency. The Mann–Whitney U test was used for intergroup comparisons of quantitative data, and the Fisher–Freeman–Halton exact test was used for intergroup comparisons for categorical variables. The cumulative probability of achieving virological response and ALT normalization rate were assessed using the Kaplan-Meier method. The difference between cumulative curves was tested using a log-rank test. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS® version 22.0; SPSS Inc., Chicago, IL, USA), and p-values ≤ 0.05 were considered as statistically significant for all analyses performed.

**RESULTS**

Twenty-nine (74.4%) patients were male, and the mean age was 48.7 ± 13.44 years. Baseline characteristics

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**Table 1: Baseline characteristics of patients included in this study**

<table>
<thead>
<tr>
<th>Baseline demographics</th>
<th>Total (n = 39)</th>
<th>HBeAg negative (n = 28)</th>
<th>HBeAg positive (n = 11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>29 (74.4%)</td>
<td>21 (75%)</td>
<td>8 (72.7%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Age (years, mean)</td>
<td>48.7 ± 13.44</td>
<td>51.96 ± 12.75</td>
<td>40.72 ± 12.16</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>Follow-up, months (median)</td>
<td>70</td>
<td>70.5</td>
<td>63</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Interferon experienced (%)</td>
<td>13 (33%)</td>
<td>9 (32.1%)</td>
<td>4 (36.4%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Nucleoside analog naive (%)</td>
<td>22 (56.4%)</td>
<td>17 (60.7%)</td>
<td>5 (45.5%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean ALT (U/L)</td>
<td>78.2 ± 57.2</td>
<td>76.3 ± 54.05</td>
<td>83.4 ± 67.1</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Median HBV DNA (log10 IU/ml)</td>
<td>5.2 ± 1.4</td>
<td>5.1 ± 1.4</td>
<td>6 ± 1.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean Knodell</td>
<td>10.15 ± 3.77</td>
<td>10.92 ± 3.47</td>
<td>8.5 ± 4.18</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean fibrosis</td>
<td>2.14 ± 1.15</td>
<td>2.26 ± 1.22</td>
<td>1.83 ± 0.98</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean fibrotest F2 score</td>
<td>2.37 ± 0.91</td>
<td>2.33 ± 1.03</td>
<td>2.5 ± 0.7</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

ALT: alanine aminotransferase; HBV: hepatitis B virus; HBeAg: hepatitis B envelope antigen
of HBeAg-positive and HBeAg-negative patients are presented in Table 1. The mean age of HBeAg-negative patients (n = 28) was significantly higher than that of HBeAg-positive patients (n = 11, p ≤ 0.05). Additionally, the median baseline HBV DNA level was significantly lower in HBeAg-negative patients than in HBeAg-positive patients (p ≤ 0.05). No significant differences in other baseline characteristics were observed between the two groups.

Twelve patients were treated with more than one drug, including ADV, LAM, interferon and pegylated interferon, prior to ETV, whereas one, four, and three patients were treated with ADV, LAM and pegylated interferon, respectively, before ETV therapy. LAM resistance was assessed in seven of a total of 14 patients who received LAM; one patient was determined to be LAM resistant.

Among a total of 39 patients who received ETV monotherapy for six years, virological response rates at 3 and 6 months and 1, 2, 3, 4, 5 and 6 years after ETV initiation were 33.3%, 54.5%, 69.2%, 82.9%, 85.3%, 96.6%, 100% and 100%, respectively. Virological response rates in HBeAg-positive and HBeAg-negative patients are shown in Fig 1. HBeAg status was not influenced by virological response (log-rank test, p = 0.416; p > 0.05).

ALT normalization rates at 3 and 6 months and 1, 2, 3, 4, 5 and 6 years after treatment initiation were 80.8%, 82.4%, 76.9%, 85.7%, 88.2%, 89.7%, 92.3% and 92.8%, respectively. ALT normalization rates in HBeAg-positive and HBeAg-negative are shown in Fig 2. HBeAg status was not influenced by biochemical response (log-rank test, p = 0.917; p > 0.05).

A total of three patients completed seven years of ETV treatment, all with maintenance of virological and biochemical responses. Among a total of 11 HBeAg-positive patients, loss of HBeAg occurred after four years of ETV treatment in only one patient, who later seroconverted during the fifth year of therapy. Loss of HBsAg was not observed in any of the patients in this study.

Virological response and biochemical response rates in NA-naive and NA-experienced patients are presented in Fig 3 and 4. Virological response was not significantly different between NA-naive and NA-experienced patients (log-rank test, p = 0.477; p > 0.05). Biochemical response was not significantly different between NA-naive and NA-experienced patients (log-rank test, p = 0.496; p > 0.05). Virological breakthrough developed in three patients after one year, in one patient after two years, in three patients after three years, and in one patient after four years of ETV treatment. Therapy switch to tenofovir dipivoxil led to virological response in 100% of these patients by week 48, which has been sustained thus far.

Comparison of patients with and without virological breakthrough revealed that there were no significant differences in age, gender, HBeAg status,
mean baseline ALT and HBV DNA values, fibrosis, and modified Knodell scores by biopsy between the two groups (p > 0.05). In our study, the cumulative rate of virological breakthrough in NA-naive and NA-experienced patients at the end of six years of ETV treatment was 9% (2 of 22) and 35.2% (6 of 17), respectively; virological breakthrough occurred significantly less in NA-naive patients than in NA-experienced patients (p ≤ 0.05).

None of the patients in this study had to discontinue treatment due to ETV-associated adverse effects, and there was no significant elevation in serum creatinine levels during the treatment period. Finally, two patients developed HCC during treatment.

DISCUSSION
Currently used therapies for CHB can rarely achieve the ideal endpoint, the clearance of covalently closed circular DNA. Thus, HBV DNA suppression, ALT normalization, HBeAg seroconversion, HBsAg loss, and histologic improvement by liver biopsy are used to assess the efficacy of antiviral therapy[12]. Persistently increased serum HBV DNA level was shown as a major risk factor for the development of HCC and cirrhosis; thus, long-term sustained HBV DNA suppression is critical for both the prevention and the reduction of CHB-associated long-term complications[13,14].

ETV and tenofovir are potent HBV inhibitors and they are recommended as first-line therapies in CHB[6]. In the study ETV-901, virological response was achieved by 94% of HBeAg positive patients over five years and in 95% of HBeAg negative patients over three years of ETV treatment[15,16]. The inclusion of selected groups of HBV patients in clinical trials complicates the translation of findings into clinical practice. Real-life studies provide better representations of everyday clinical practice and are important to confirm the results reported in clinical studies[17]. In real life studies of ETV, up to five years of treatment resulted in virological response in 76 - 100% of patients with CHB respectively[17–22]. Previous studies evaluating the long-term outcomes of ETV treatment among HbsAg-positive and HBeAg-negative patients reported virological response that were similar to those found in the present study with one distinction, whereas all patients in previous studies were NA-naive, our study included both NA-naive and NA-experienced patients with CHB. When the real-life data is considered, it is known that the NA analogs such as LAM and ADV were widely used in the past and is still being used in some countries today.

An increasing number of patients who experienced treatment failure with different NA-treatment regimens constitutes an important problem for clinicians. Discontinuation of therapy...
because of inadequate response or resistance to NA-treatments, noncompliance and financial barriers poses a growing problem in daily practice\cite{19}. Therefore, we consider that our study is important to determine the treatment alternatives for this group of patients, since it contains NA-experienced patients and shows the long-term results. In studies evaluating the outcomes of ETV treatment in NA-experienced patients, lower virological response were observed in both HBeAg-positive and HBeAg-negative patients in contrast to those found in NA-naive patients\cite{23,24}. Al-Ashqar et al. indicated that the low virological response rate observed in their study might be multifactorial and concluded that their findings were associated with antiviral use prior to ETV treatment, excessive number of HBeAg-positive patients, and low treatment compliance\cite{25}. Similarly, the virological response rate in our study was lower in HBeAg-positive patients than in HBeAg-negative patients; albeit not statistically significant, the comparatively higher rate of NA-experienced patients in this group compared with that of HBeAg-negative patients could impact virological response. In previous studies, the 1- and 2-year virological response rates were assessed in cohorts that included NA-experienced patients, whereas we determined virological response after six years of ETV treatment in both NA-naive and NA-experienced patients in the present study.

ETV is a potent antiviral with a high genetic barrier to resistance in NA-naive patients. The antiviral efficacy of ETV was not influenced by prior treatment with ADV\cite{11}. However, ETV treatment is less effective in LAM-refractory patients compared to NA-naive patients\cite{25}. Reijnders et al. showed that efficacy of ETV is significantly decreased in patients with LAM-resistance\cite{11}. In our study, virologic breakthrough rate was statistically more frequent in NA-experienced patients. When NA-experienced patients with virological breakthrough were evaluated, we detected that they all had LAM experience. We couldn’t analyze LAM resistance in all of the LAM-experienced patients in our study. Consequently, higher virologic breakthrough rates in our LAM-experienced patients may be due to possible LAM resistance.

Previous studies evaluating biochemical response rates with ETV treatment were conducted only in NA-naive patients\cite{17-22}. Although our findings on biochemical response rates were consistent with previous findings, one particular strength of our study is the exclusive evaluation of these parameters after six years of ETV treatment in a cohort containing not only NA-naive but also NA-experienced patients.

**CONCLUSION**

Data on the efficacy in NA-experienced patients are limited. One major strength of this real-life study is the evaluation of long-term outcomes of ETV treatment in both NA-naive and NA-experienced patients with CHB. Our findings suggest that LAM resistance should be considered before initiation of ETV treatment in all patients with a history of LAM experience due to the high virological breakthrough. However, our experience with NA-naive patients demonstrated that high viral suppression could be achieved with six years of ETV treatment.

**REFERENCES**


Awareness of Diabetic Eye Disease among Diabetics: The Enugu Diabetes Eye Care Study, Report 2

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ABSTRACT

Objective: Globally, diabetic eye disease (DED) remains a public eye health issue. Identifying patient-level factors associated with DED awareness is critical for its prevention and management. This study aimed to determine the prevalence and associations of awareness of DED in a Nigerian hospital-based diabetic population.

Design: Questionnaire-based cross-sectional survey

Setting: Diabetic clinic of the University of Nigerian Teaching Hospital (UNTH), Enugu from February to March 2012

Subjects: Adult outpatient diabetics aged 18 years or older

Intervention: Non-interventional

Main outcome measure: Awareness of diabetic eye disease

Results: The participants (n = 233; males = 105) were aged 59.3 ± 13.5SD years (range: 24 - 99 years). The majority were married (94%), had formal education (79.4%), traders (29.2%) and resided in urban areas (67%). One hundred and eighty eight (80.4%) participants were aware that diabetes can affect the eyes and possibly cause blindness. Their main sources of awareness were clinic-based health talk (69.1%) and the doctor providing diabetic care (5.2%). Current visual problem (odds ratio (OR): 0.39; 95% confidence interval (CI): 0.18 - 0.83, p = 0.019) and previous dilated fundus examination (DFE) (OR: 2.69; 95% CI: 1.31 - 5.53, p = 0.009) were the significant predictors of DED awareness.

Conclusion: There is a high prevalence of DED awareness among diabetics at UNTH, Enugu. Clinic-based health talk and physician-provided health education are the main sources of awareness. Current visual problem and previous DFE are the significant predictors of awareness of DED. Further enrichment and expansion of scope of nurse- and physician-provided hospital-based diabetes-related eye health education are warranted.

INTRODUCTION

Worldwide, about 382 million people live with diabetes mellitus (DM) in the year 2013 and this is projected to increase to 592 million by 2035[1]. In Africa, the estimated prevalence of diabetes is 1% in rural areas, and up to 7% in urban sub-Saharan Africa[2]. Epidemiological data from the World Health Organization (WHO) suggest that, in Africa, Nigeria has the highest burden of DM[3], with an estimated prevalence of 3.3 - 10%[4,5]. The health burden associated with DM is mainly due its complications: hyperglycaemic emergencies[6], cardiovascular accidents and nephropathies[7,8], neuropathies[9] and retinopathies[10,11].

Diabetic eye disease (DED) encompasses a spectrum of diabetic eye complications including diabetic retinopathy (DR), cataract, diabetes-related shifts in refraction status and recurrent corneal erosion[5]. DR, the leading cause of vision loss in diabetics, accounts for 16.2% to 42.1% of retinal diseases in Nigeria[10,11]. Globally, DR accounts for 5% of blindness[12]; in Nigeria, it accounted for 0.5% of blindness[3]. The prevalence of DR among diabetics differ by country, being 29.9% in Malaysia[13], 23% in India[14] and 20.5% in Nigeria. However, these differences have to be interpreted with caution as it is influenced by between-survey differences in sample populations, sensitivity of examination methods and examiner experience[9]. Across these studies[10,11,13,14], co-morbid hypertension and poor glycaemic control were the identified predictors of developing DR. People with DM were also found to be over three folds more likely to become blind than those without DM[3].

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The prevalence of DR is comparatively higher in hospital-based studies: Malaysia - 86%[13], India - 84%[14], Myanmar - 86%[15], Turkey - 88.1%[16], and USA- 65%[17], than in population-based surveys: Australia - 37%[18], rural - 37.1%[19] and urban - 27%[20] to India. The identified predictors of awareness of diabetic eye disease were high literacy level[13,15,16,19], longer duration of DM[15,16] and previous visit to an ophthalmologist, but not an optometrist or a general practitioner[13].

The reported sources of awareness are clinic-based health education[13,21] by the eye specialists, general practitioners, physicians or nurses, and the mass media. Given the current global pandemic of DM and the increasing life expectancy of diabetics, the prevalence of diabetic eye disease is bound to increase[22]. Blindness from DM is preventable through early detection and prompt treatment of diabetic eye disease[23]. Awareness of diabetic eye disease among diabetics is critical for preventing diabetes-related blindness. In Nigeria, there is paucity of research data on awareness of diabetic eye disease among diabetics. Consequently, this study set out to generate evidence-based data to guide the provision of diabetic eye care interventions.

SUBJECTS AND METHODS
Background: The University of Nigeria Teaching Hospital (UNTH), Enugu, established in 1971 and located in Nigeria’s south-east geopolitical zone, provides tertiary healthcare services to the public. At UNTH, a dedicated Diabetic Clinic in the Medical Outpatient section provides clinical care and diabetic health education for diabetics. After their consultation at the Diabetic Clinic, diabetics in need of eye care are referred to the UNTH’s Eye clinic for ophthalmic evaluation. The present study, conducted in February and March 2012, was a cross-sectional questionnaire-based survey of adult outpatients with diabetes attending the Diabetic clinic in UNTH, Enugu.

Ethics: Prior to commencement of the study, ethics clearance, compliant with the 1964 Helsinki Declaration, as amended in London in 2008, on research involving human subjects, was obtained from the UNTH’s Medical and Health Research Ethics Committee (Institutional Review Board). Additionally, informed consent to participation, without any inducement, was obtained from each participant.

Eligibility: Adults (≥ 18 years) attending UNTH’s diabetic clinic, who were diagnosed with type 1 or type 2 DM by a diabetologist

Exclusion criteria: Patients with diagnosis of gestational or drug-induced diabetes, and those who withheld voluntary consent to participation

Operational definitions: DM was defined according to the WHO criteria as fasting venous plasma glucose ≥ 7 mmol/L (126 mg/dl) on two different days[24]. Awareness of diabetic eye disease: respondent’s reported awareness that ‘Diabetes can affect the eyes and possibly cause blindness’. Formal education: possession of at least primary education. Blindness: presenting distance visual acuity less than 3/60 in the better eye.

Study questionnaire: The study instrument was a 21-item, researcher-administered, self-report questionnaire with fields on participants’ socio-demographics, diabetes and ophthalmology. The diabetes subsection sought participants’ data on type of diabetes, duration, treatment, and associated systemic co-morbidities. The ophthalmology subsection sought data on participants’ self-reported visual complaint, prescription spectacle wear, awareness of diabetic eye disease and the sources of this awareness. To ascertain its construct validity and internal consistency reliability, the questionnaire was pretested on a cohort of adult diabetic outpatients, under similar study settings, outside the study centre. The final version of the questionnaire had an internal consistency reliability coefficient (Cronbach alpha coefficient) of 0.75 and Lawshe’s content validity index of 0.7.

Sample size and Sampling: This survey was a sub-study from the ‘The Enugu Diabetes Eye Care Study’. Consequently, the sample size of 233 was based on 28.9% prevalence of compliance with annual diabetic screening eye examination previously reported in a Nigerian study[25]. A comprehensive diabetes register, which would have served as a sampling frame, was not available at the time of study. Consequently, eligible and consenting participants were randomly selected, from a register generated each day by the investigators, and interviewed on the same clinic day, until the required sample size was obtained.

Randomisation technique: Based on the calculated sample size of 233 and a 2-month anticipated duration of the study, i.e., 8 once-a-week diabetologist-run Diabetic clinic days, 30 (233/8 = 29.125) participants were recruited each clinic day as follows: the number of patients registered each day (population size) was divided by 30 (daily sample size) to get the sampling interval or skip interval (k). After a random start, every kth name in the register was selected for recruitment until the required daily sample size was obtained. A repeat drawing was prevented by specifically instructing each recruited participant to decline future invitation to participate in the same study.
Data analysis: Data was entered into and analysed using the Statistical Package for Social Sciences (SPSS) software for windows, version 18 (SPSS Inc, Chicago, Illinois, USA). Data were statistically described in terms of mean ± SD, frequencies, percentages and proportions. Between-group comparisons, to test for significance of observed intergroup differences, were performed using the Student-t test for metric variables and Chi-squared test or Fishers’ exact test for categorical variables. In all comparisons, a p-value < 0.05 was considered statistically significant. Significant predictors on bivariate analysis were entered into a multivariate logistic regression model to assess their independent predictive effect on the outcome of interest, awareness of diabetic eye disease.

RESULTS
Socio-demographic characteristics
The study had 233 participants comprising 105 males and 128 females (sex ratio = 1:1.2) who were aged 59.3 ± 13.5 SD years (range: 24 - 99 years) with a modal age group of 58 - 67 years (Table 1).

Table 1: Participants’ demographic profile

<table>
<thead>
<tr>
<th>Age group (Years)</th>
<th>Sex</th>
<th>n (%) N = 233</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 - 27</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>28 - 37</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>38 - 47</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>48 - 57</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>58 - 67</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>68 - 77</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>78 - 87</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>88 - 97</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>98 - 107</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total (%)</td>
<td>105</td>
<td>128 (54.9)</td>
</tr>
</tbody>
</table>

M: male; F: female

The difference between the mean ages of males and females was statistically significant (male Vs female: 62.7 ± 12.8 Vs 56.4 ± 13.5, t = 3.591, p = 0.0003). The respondents were predominantly married (219, 94%), possessed formal education (189, 79.4%), traders (68, 29.2%) or farmers (32, 3.7%), and resided in the urban areas (156, 67%) (Table 2).

Clinical profile
Two hundred and six (88.4%) participants did not know their type of diabetes; the majority (209, 89.7%) have had diabetes for 15 years or less. Positive family history of DM was reported by 78 (33.5%) participants. The respondents’ types of anti-diabetic therapy were oral hypoglycaemic treatment (129, 59.4%), diet therapy (64, 27.5%) and insulin (40, 17.2%). Eighty two (35.2%) participants had concurrent chronic systemic co-morbidity. The participants’ clinical profile is shown in Table 3.

Eleven (4.7%) participants reported current visual problems with their near or distant vision while 68 (29.2%) had difficulty with both. Previous or current use of prescription spectacles was reported by 102 (43.7%) respondents.

Awareness of diabetic eye disease
One hundred and eighty eight (80.4%) participants were aware that diabetes can affect the eyes and
possibly cause blindness. Their sources of awareness were nurse-delivered clinic-based health talk (161, 69.1%), the doctor (12, 5.2%), fellow DM patients (6, 2.6%), family members and friends (5, 2.1%) and mass media (radio/TV/newspaper – 3, 1.3%).

None (0%) of the participants’ socio-demographic characteristics was significantly associated with their awareness of diabetic eye disease. Of their clinical characteristics, only ‘current visual problem’ (odds ratio (OR): 0.39; 95% confidence interval (CI): 0.18 - 0.83, p = 0.019) and ‘previous dilated fundus examination (DFE)’ (OR: 2.69; 95% CI: 1.31 - 5.53, p = 0.009) significantly predicted participants’ awareness of diabetic eye disease (Table 4).

**DISCUSSION**

The participants comprised of more females than males who were aged 59.3 ± 13.5 SD years. The majority were married, possessed formal education, and were predominantly traders. This socio-demographic profile is similar to the findings in related hospital-based studies in Ghana, Malaysia and Turkey, but differs from the results of population-based surveys in Australia and India. The similarity in study settings between the present study and the Ghanaian, Turkish and Malaysian surveys, and its contrast to the population-based Australian and Indian studies probably explains the observed similarities and differences. In addition to providing contextual and comparative data, participants’ socio-demographic profile guides logistical interventions to optimise uptake of diabetes care. Consequently, the investigators recommend that future surveys provide these critical background data on study participants.

The majority of the participants have had DM for less than fifteen years with oral hypoglycaemic agents as their main anti-diabetic treatment modality. About one-third had a family history of DM; hypertension was their leading systemic co-morbidity. The observed clinical characteristics corroborate the findings at Korle-Bu Teaching Hospital, Ghana and in Kano, Nigeria. Further between-survey comparisons were precluded by the non-reporting of participants’ background clinical data in most of the related previous reports.

These studies share similar socio-economic settings with the present study, typically seen in low and

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**Table 4: Factors associated with respondents’ awareness of diabetic eye disease**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Awareness of Diabetic eye disease</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (%)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>N = 233</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Socio-demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (%)</th>
<th>Yes</th>
<th>No</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (Yes/No)</td>
<td>181 (77.7)</td>
<td>54.9 ± 13.2 SD t = 0.38</td>
<td>(-3.64 - 5.35)</td>
<td>0.708</td>
<td></td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>44 (18.9)</td>
<td>58.6 ± 15.1 SD</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>105 (45.1)</td>
<td>83 (79)</td>
<td>22 (21)</td>
<td>0.83 (0.43 - 1.59)</td>
<td>0.684</td>
</tr>
<tr>
<td>Possess formal education (Yes/No)</td>
<td>128 (54.9)</td>
<td>105 (82)</td>
<td>23 (18)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Occupation status (Employed/Unemployed)</td>
<td>185 (79.4)</td>
<td>145 (78.4)</td>
<td>40 (21.6)</td>
<td>2.37 (0.88 - 6.39)</td>
<td>0.122</td>
</tr>
<tr>
<td>Residence (Urban/Rural)</td>
<td>188 (80.7)</td>
<td>125 (66.5)</td>
<td>63 (33.5)</td>
<td>1.45 (0.75 - 2.82)</td>
<td>0.355</td>
</tr>
<tr>
<td>Current visual problem (Yes/No)</td>
<td>188 (80.7)</td>
<td>108 (57.4)</td>
<td>80 (42.6)</td>
<td>0.39 (0.18 - 0.83)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Spectacle wear</td>
<td>136 (58.4)</td>
<td>106 (77.9)</td>
<td>30 (22.1)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Ever had a DFE (Yes/No)</td>
<td>128 (54.9)</td>
<td>95 (74.2)</td>
<td>33 (25.8)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Regular DFE (Yes/No)</td>
<td>168 (72.5)</td>
<td>131 (77.5)</td>
<td>38 (22.7)</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Diabetes (Years) ≤ 15 vs &gt;15</td>
<td>0.16 (0.02 - 1.24)</td>
<td>0.087</td>
</tr>
<tr>
<td>Family history of Diabetes (Yes/No)</td>
<td>1.71 (0.82 - 3.59)</td>
<td>0.164</td>
</tr>
<tr>
<td>Type of orthodox therapy (Insulin/OHA)</td>
<td>2.37 (0.88 - 6.39)</td>
<td>0.122</td>
</tr>
<tr>
<td>Associated systemic disease (Yes/No)</td>
<td>1.45 (0.75 - 2.82)</td>
<td>0.355</td>
</tr>
<tr>
<td>Current visual problem (Yes/No)</td>
<td>0.39 (0.18 - 0.83)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Spectacle wear</td>
<td>1.55 (0.78 - 3.07)</td>
<td>0.276</td>
</tr>
<tr>
<td>Ever had a DFE (Yes/No)</td>
<td>2.69 (1.31 - 5.53)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Regular DFE (Yes/No)</td>
<td>2.36 (0.99 - 5.61)</td>
<td>0.071</td>
</tr>
</tbody>
</table>

*: Significant; DFE: Dilated Fundus Examination; OHA: Oral hypoglycaemic agent; OR: odds ratio; CI: confidence interval
middle-income countries (LMICs). Consistent with the present report, several studies\textsuperscript{26-30} have demonstrated associations between DM and positive family history of DM and hypertension. As previously suggested, the present data also underscore the need for reporting participants’ background clinical data. This would inform planning strategies for holistic medical care for diabetics.

The prevalence of awareness of diabetic eye disease in the present study is 80.4%; clinic-based health talk is the main source of awareness (69.1%). This awareness level is comparable to reports in Malaysia (86\%)\textsuperscript{13}, India (84\%)\textsuperscript{14}, Myanmar (86\%)\textsuperscript{15}, Turkey (88.1\%)\textsuperscript{16} and elsewhere in Nigeria (84.3\%)\textsuperscript{27}. However, it is comparatively higher than the findings from population-based surveys in Australia (37\%)\textsuperscript{18}, rural (37.1\%)\textsuperscript{19} and urban (27\%)\textsuperscript{20} India. The observed similarities are attributable to the hospital-based design of these studies\textsuperscript{13-16,27}, where patients routinely receive pre-consultation clinic-based diabetic health talk, the main source of awareness in the present report. This highlights the need for dedicated periods for clinic-based diabetic health education, especially on diabetic eye disease. Towards this end, settings-appropriate health education materials should be provided to facilitate effective and efficient health communications between care provider and diabetics.

In this study, current visual problem and DFE did, while participants’ socio-demographic and other clinical characteristics did not, significantly predict awareness of diabetic eye disease. These corroborate the findings in Ghana\textsuperscript{26} and Nigeria\textsuperscript{27} but are in contrast with the Malaysian\textsuperscript{13}, Turkish\textsuperscript{16}, Myanmar\textsuperscript{15} and Indian\textsuperscript{19} reports, where high literacy level and duration of DM\textsuperscript{15,16} were the significant predictors of awareness. While the hospital-based designs of the present survey, the Ghanaian\textsuperscript{26} and Nigerian\textsuperscript{27} studies might explain the observed similarities, between-survey variations in participants’ socio-demographic and clinical characteristics probably explain the observed differences. To further enhance awareness, diabetic care providers should inquire about eye health status of diabetics and encourage their compliance with guidelines-recommended periodic DFE.

The generalisation of the findings of this study is limited by its hospital-based one-centre design and reliability issues inherent in patient-reported data.

CONCLUSION

There is high awareness of diabetic eye disease among diabetic outpatients at UNTH, Enugu. Nurse-provided clinic-based health talk was the main source of awareness. Current visual problem and previous DFE were the predictors of awareness of diabetic eye diseases. Strengthening and expanding the scope of clinic-based health education and establishment of multi-specialty diabetic clinic would further enhance awareness.

ACKNOWLEDGMENTS

The authors wish to acknowledge the assistance of the staff of the UNTH’s Diabetic Clinic during data collection.

Authorship: All the listed authors contributed significantly to conception and design of study, acquisition, analysis and interpretation of data and drafting of manuscript, to justify authorship.

REFERENCES


Original Article

The Role of Sucralfate in the Treatment of Nasal Synechia

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2Department of Otorhinolaryngology, Numune Education and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: Synechia is an important and frequently encountered complication of nasal surgery. Recurrent synechia can be seen after synechia correction surgeries. Sucralfate has recently come up with its topical use in healing epithelial wounds.

Design: Retrospective analyses of prospective recorded data

Setting: Department of Otorhinolaryngology, Numune Education and Research Hospital, Ankara, Turkey

Subjects: Records of 16 patients who had previously undergone nasal surgery were investigated. Nasal synechia was detected in their controls and they underwent surgery for synechiae correction. During the synechiae correction surgery of 16 patients, topical sucralfate was used in 11 different synechiae regions in nine patients in group A and in the control group (Group B), it was not used in 9 separate regions in 7 patients.

Interventions: Nine patients in group A received topical sucralfate. Seven patients in group B had surgery without topical sucralfate.

Main outcome measure: We have investigated the effect of topical application of sucralfate on the success of nasal synechia correction surgery.

Results: Recurrent synechia wasn’t detected in group A, treated with topical sucralfate, whereas in the control group, seven patients had recurrent synechia in three of the nine separate regions. When statistically analyzed, recurrence is seen to be much lower in group A.

Conclusion: In conclusion, topical use of sucralfate in synechia correction surgery applied in cases of postoperative nasal synechiae increases the success rate of surgery.

KEY WORDS: nasal surgery, postoperative complications, sucralfate, synechia, topical

INTRODUCTION

Synechia is defined as fibrosis in the parts of an organ[1]. Trauma can develop in different regions of the nasal cavity due to endonasal surgery and infection[2-4]. It is a common and important complication of nasal surgery, such as functional endoscopic sinus surgery (FESS), septoplasty and septorhinoplasty. Despite meticulous postoperative care and dressing, synechia is seen in a significant proportion of patients. Early synechiae are often seen between the middle turbinate and the lateral nasal wall during postoperative dressings[5,6]. When synechia occurs in the middle meatus, it can create problems by causing congestion in the maxillary, ethmoid and frontal sinus[6]. Nasal congestion may also occur in case of the presence of synechia between septum and turbinates in the nasal cavity. Surgery may be needed to ensure normal sinus drainage and breathing pattern. After nasal surgery, Merocel, FloSeal, Sepragel, hyaluronic acid and topical mitomycin C were used to reduce synechia complications and improve surgical success[7-9]. Common complication of the synechia correction surgery is the development of recurrent synechia. Topical mitomycin C has been used after both nasal surgeries and nasal synechia correction surgeries to prevent recurrence[10].

Sucralfate is a pharmaceutical agent used in the treatment of gastric and duodenal ulcers and preventing their recurrence, in the treatment of gastritis, esophagitis and stress ulcers with cytoprotective property. In addition, it accelerates superficial epithelial cell regeneration and increases the resistance of the mucosa[11]. In the treatment of nasal synechiae, there is no study in the literature regarding the use of sucralfate.

This study has investigated the effect of topical sucralfate on the risk of recurrent synechiae in surgeries for synechia correction.

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MATERIALS AND METHODS
Records of 16 patients who were operated between September 2010 and January 2013 due to the complaint of nasal congestion and recurrent postnasal discharge were retrospectively analyzed, and nasal synechia was detected in their endoscopic examination and hence underwent synechia correction surgery.

Sucralfate applied patients were examined in group A, and the unapplied ones in group B. Group A consisted of nine patients and group B contained the remaining seven patients included in the study.

Nasal synechia regions of these patients were revealed in their endoscopic examination (Fig 1).

Exclusion criteria for the study include diabetes, systemic autoimmune disease, smoking habits, diagnosed allergic respiratory disease and patients with acute upper respiratory tract infection. Inclusion criteria were patients who had previously undergone septoplasty and/or endoscopic sinus surgery, synechiae detected between the septum and inferior turbinate and/or septum and middle turbinate.

Synechiae of the patients in group A were opened lengthways under local anesthesia with the help of a lancet after the injection of lidocaine HCl 20 mg/ml and epinephrine HCl 0.0125 mg/ml into the synechia regions (Fig 2).

1 gr of sucralfate tablet was powdered and applied on the incision region of synechia (Fig 3).

To prevent any contact between the opposite mucous membranes, a plug prepared in roentgen film sheets and passed by suture through its rear end was placed into the opened synechia region, fixed on the nasal ridge with plaster and kept there for a week (Fig 4). All steps, except for topical sucralfate application, were applied in the same way to the patients in group B.

In both groups, no complications were seen in the early postoperative period. At the end of the first week, patients were taken under follow up by pulling out the plastic plug. Whether the patients had postoperative recurrent synechia was evaluated in the 1st and 3rd months of their follow up (Fig 5).
Statistical Analysis
Data analysis was performed using SPSS for Windows 14.0 package program. Mann Whitney U-Test, chi-square and t-test were used for statistical analyses. Results were considered significant if the p-value was < 0.05.

RESULTS
Of the nine patients in group A, 45% were male and 55% were female. The average age was 37.8 with an age range of 19 to 60. Four (45%) of these patients had undergone septoplasty and FESS, four (45%) only had septoplasty and one (10%) only had FESS. The patients underwent preoperative endoscopic examination. In their endoscopic examination, left sided synechia was detected in five (55%) patients, right sided synnechia in two (22.5%) patients and bilateral synnechia in the remaining three (22.5%) patients. Seven patients had synnechia only in one region, while two patients had it in more than one region. In the total of nine patients, synechia was detected in 11 different regions. Synechia was observed mostly in seven (64%) different regions between septum and inferior turbinate; four (36%) between septum and middle turbinate.

In group B, 57% of the 10 patients were female, 43% were male. The average age was 37.4 and with an age range of 23 to 59. One (14%) of these patients had undergone septoplasty and sinus surgery, five (72%) only had septoplasty and the remaining one (14%) had FESS. In their endoscopic examination, left sided synnechia was detected in three (42%) patients, right sided synnechia in two (29%) patients and bilateral synnechia in two (29%) patients. In the total of seven patients, synnechia was detected in nine different regions. Synnechia was observed mostly in eight (89%) different regions between septum and inferior turbinate; one (11%) between septum and middle turbinate.

In the controls of group A, recurrent synnechia was not observed in any patient.

Recurrent synnechia was not seen in six (67%) of the nine different regions in four (57%) of the seven patients in Group B. Recurrent synnechia was seen in three regions between septum and inferior turbinate.

When groups A and B were statistically compared in terms of recurrent synnechia, it was seen significantly less in group A, in which topical sucralfate had been applied (p = 0.043).

In group A, recurrent synnechia was not observed in any patient. In group B, three recurrent synnechia were detected in the area of septum-inferior turbinate while none were seen between septum and the middle turbinate in both groups.

DISCUSSION
By the convergence of the damaged mucosal surfaces after the sinonasal surgery, regenerated epithelium and fibrous tissue develop between these surfaces and create synnechia. The main causes of synnechia development during surgery are inadequate protection of the mucosa and leaving open mucosal surfaces, thus leading them to stick together through contact. Additionally, existence of pneumatization in the middle turbinate facilitates synnechia formation by allowing the mucosa to contact with the lateral nasal wall.[12]. If the synnechia is of sufficient size and in appropriate position, it can lead to sinus infection by causing obstruction in the adjacent sinus ostium, or to breathing problems by forming congestion in the nasal passage.

The most effective measures to prevent synnechia occurrence can be listed as mucosal protection during surgery, careful postoperative care and dressing of surgical wounds. Materials such as Merocel, FloSeal, Sepragel and hyaluronic acid have been used to prevent the development of synnechia after surgery.[8,9]. Mitomycin C has also been used to prevent postoperative complications by inhibiting fibrosis.[9].

Recurrent synnechia is considered as the most important complication after synnechia correction surgery due to nasal synnechia. To reduce the risk of recurrent synnechia, there are studies conducted on topical mitomycin C application.[10]. Due to its antiproliferative properties, mitomycin C is thought to reduce the incidence of synnechia after sinonasal surgery. In a study in which diode laser and topical mitomycin C were used for the treatment of nasal synnechae, Hesham et al.[10] have reported the application to be a simple, safe and effective approach. Anand et al.[13], however, have mentioned in a study that mitomycin C has no statistical effect on the development of synnechia after endoscopic sinus surgery. To assess the long term safety and efficacy of
adjunctive mitomycin C treatment in endoscopic revision dacryocystorhinostomy surgery, Görgülü O et al\textsuperscript{[14]} reported that adjunctive intra-operative mitomycin C application had a good success rate in patients with nasolacrimal duct obstruction that required revision surgery.

Chung JH et al\textsuperscript{[15]} reported that mitomycin C was found to be safe to use during sinus surgery, and it may reduce the incidence of postoperative adhesions. Numthavaj P et al\textsuperscript{[16]} also stated that applying mitomycin C topically after endoscopic sinus surgery could reduce the risk of nasal synechiae and maxillary sinus ostium stenosis in short term by 66% and 74%. Further trials with good research methodology and long-term follow-up were recommended.

There are some studies on the use of various materials in the treatment of nasal synechiae, whereas there isn’t any on the use of sucralfate. It contains basic aluminum sucrose sulfate. It is a pharmaceutical agent, generally administered orally in the prevention and treatment of various gastrointestinal diseases such as gastroesophageal reflux, gastric and duodenal ulcers. In recent studies, sucralfate has come up with its effect on accelerating epithelial cell regeneration by increasing natural defense factors of the mucosa, we have investigated the effect of sucralfate, which shows cytoprotective property in the treatment of nasal synechiae, on the risk of recurrent synechiae.

Records of 16 patients who had undergone synechia surgery after their sinonasal operation were examined in this study. Nine patients had topical sucralfate applied in their synenchia correction operation, whereas seven patients in the control group had the same procedure without using topical sucralfate. Topical sucralfate implementation dependent patients did not develop any complications. When the results in both groups were compared, surgical success was seen more in the group treated with topical sucralfate and recurrent synechia development was statistically lower. We have seen that application of topical sucralfate together with surgery is an effective approach in nasal synechia treatment against the risk of recurrent synechia.

CONCLUSION

With its effect on accelerating epithelial cell regeneration, topical sucralfate application is a really safe, effective and easily applicable method that increases surgical success in surgical correction of nasal synechiaeae.

REFERENCES

Original Article

Anthropometric, Clinical and Biochemical Comparison of the Four Polycystic Ovarian Syndrome Phenotypes

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ABSTRACT

Objectives: Polycystic ovarian syndrome (PCOS) phenotypes in different races and ethnicities present with various features. This study aimed to investigate the anthropometric, clinical and biochemical differences according to the four Rotterdam phenotypes of PCOS.

Design: A cross-sectional study was conducted.

Setting: Two private infertility clinics and a public endocrinology clinic in Rasht, Iran

Subjects: One hundred and sixty one women with PCOS aged between 15 and 41 years from March 2010 to July 2012 were included. Polycystic ovarian syndrome was diagnosed by irregular menstruation (IM), polycystic ovary (PCO) and hyperandrogenism (HA).

Intervention: Demographic data, and fertility features were collected and anthropometric, clinical and biochemical characteristics were measured.

Main outcome measures: There were significant differences in mean levels of 17-hydroxyprogesterone (P = 0.010), luteinizing hormone (P = 0.047), and ratio of luteinizing hormone / follicle stimulation hormone (P = 0.017) among the four phenotypes.

Results: Most of the subjects were categorized into the IM + PCO + HA phenotype (54%), followed by IM + HA (28%), IM + PCO (13%), and PCO + HA (5%). Among the four phenotypes, there were no significant differences in terms of demographic characters, fertility features and anthropometric measurements (P > 0.05), but there were significant differences in the prevalence of hirsutism, alopecia and morphology of PCO (P < 0.05).

Conclusion: Phenotypes of PCOS in women from Rasht are similar in most anthropometric, clinical and biochemical features.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a prevalent endocrinopathy in women of reproductive age. The prevalence of PCOS is reported at 5 - 10% based on the applied diagnostic criteria[1,2]. This syndrome has some clinical complications including infertility, hyperandrogenism, hirsutism, metabolic disorders (android obesity), high prevalence of metabolic syndrome, high blood pressure, insulin resistance, fatty liver, higher risk of cardiovascular disease and endometrial cancer, as well as biochemical complications such as dyslipidemia, hyperlipidemia [increased lipids in the blood, including cholesterol, low density lipid (LDL) and triglycerides (TG) and decreased high density lipid (HDL)][2-5].

Annually, a considerable amount of governments' health budget is spent on PCOS related complications. This burden includes costs related to PCOS-associated diabetes mellitus type 2, hormonal treatment of menstrual disorder, infertility and hirsutism treatment. Screening for early detection of metabolic disorders in this group of women is recommended[6]. Moreover, identifying potential high risk PCOS phenotypes for effective screening and interventions of metabolic diseases is essential[7].

In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) held a conference in Rotterdam about PCOS. It was recommended that the morphology of polycystic
ovaries (PCO) observed during an ultrasonographic examination be added to the diagnostic criteria. Based on the Rotterdam criteria, PCOS is diagnosed when two of the following features are presented: irregular menstruation (IM), clinical or laboratory hyperandrogenism (HA) and morphology of PCO from an ultrasonographic examination with the absence of any of the following disorders: hypothyroidism, Cushing’s syndrome, Congential Adrenal Hyperplasia (CAH), hyperprolactinaemia or androgen secreting tumors[8].

Various studies were carried out in different regions of the world and they reported different features of PCOS. PCOS in different race and ethnicity are presented in various features[9]. In different regions of Asia, there are differences in anthropometric, clinical and biochemical features of different phenotypes of PCOS. Among PCOS women from the Middle East, which includes Iran, it is reported that there is a higher prevalence of hirsutism[10-12]. In Iran and other Middle Eastern countries, there are few studies that have assessed the characteristics of different phenotypes of PCOS based on the 2003 Rotterdam criteria. This study aimed to investigate anthropometric, clinical, and biochemical differences according to the four Rotterdam phenotypes of PCOS in Rasht, in the north of Iran.

SUBJECTS AND METHODS
Setting and patients
A prospective cross-sectional study was conducted on women with PCOS aged 15 – 41 years, from March 2010 to July 2012. The study was approved by the Ethical Committee of the Guilan University of Medical Sciences, and all subjects provided written informed consent.

During the study period, all women who attended two private infertility clinics and a public endocrinology clinic in Rasht with a main complaint of menstrual disturbances or signs of hyperandrogenism were evaluated for PCOS. Menstrual disturbance was defined as oligomenorrhea (menstrual cycle with intervals of more than 35 days or less than 9 cycles in a year) or amenorrhea (absence of a cycle for more than 3 months). Clinical HA was defined as the presence of hirsutism or acne. Exclusion criteria were CAH, androgen secreting tumors, Cushing’s syndrome, abnormal thyroid function test, hyperprolactinaemia, 17-hydroxyprogesterone (17-OHP) > 3 mg/ml, and androgenic/anabolic drug use or abuse.

According to the 2003 Rotterdam criteria, the diagnosis of PCOS was based on the presence of at least 2 out of 3 criteria: (i) oligomenorrhea and/or anovulation (menstrual cycle > 35 days), (ii) HA (either clinical or biochemical) and (iii) PCO and exclusion of other etiologies. Based on these criteria, the four phenotypes can be classified as: type 1: IM + PCO + HA, type 2: IM + HA, type 3: IM + PCO, and type 4: PCO + HA[8].

Measurement of anthropometric, clinical and biochemical features
Biochemical HA was defined as serum testosterone above 2 standard deviation of the mean range for reproductive-aged women in the control group with normal morphology (transvaginal ultrasound) and the absence of HA or menstrual disturbances.

In this study, hirsutism was defined as the presence of excess terminal hair in the upper lip, chin, chest, abdomen, groin, back and upper arms. A gynecologist and endocrinologist considered the Ferriman-Gallwey score ≥ 8 as hirsute. The presence of pustules or comedones on the face, neck, upper chest, back and arms were considered as acne. Ovarian volume was measured using the 0.5*width*length*height formula. However, in patients with follicular cyst > 12 mm, ovarian volume was not detected. We measured free testosterone, dehydroepiandrosterone sulfate (DHEAS), 17-OHP (to rule out CAH), thyroid-stimulating hormone (to rule out thyroid dysfunction), and prolactin (to rule out prolactinoma). We also measured the luteinizing hormone (LH), follicle stimulation hormone (FSH), total cholesterol, TG, HDL, LDL, fasting blood sugar (FBS), 2-hour postprandial (2HPP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

All subjects were referred to a predetermined laboratory. Blood samples from the subjects were taken during days 3 - 5 of their cycle or after a withdrawal bleed in oligomenorrhoic and amenorrhoic women (10 cc venous blood after 12-hour fasting). We assessed FSH and LH by immunoassay access 2 (Beckman, Fullerton, California, USA), free testosterone, DHEAS and 17-OHP by access RIA (Simens, Los Angeles, CA, USA) and thyroid-stimulating hormone (TSH) by the Chemiluminescence immunoassay kit (Immulite 2000 Analyzer; CPC, Los Angeles, CA, USA). We also used the fasting blood sample to measure the FBS (by Hitachi 7600), cholesterol, TG, AST, ALT, HDL and LDL (by enzymatic calorimetric Hitachi 7600) and 2HPP was evaluated by a 75 g glucose tolerance test using glucose (Pars Azmon, Iran). Prolactin was measured by ELISA (Padtan Elam, Iran).

All transvaginal ultrasonographies were performed by an experienced sonographer and for subjects who were not married, abdominal sonographies were performed.

Age, marital status, family history of diabetes, fertility features (parity, history of infertility as defined by an experienced sonographer and for subjects who were not married, abdominal sonographies were performed.

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by the absence of pregnancy for at least one year without using contraception methods), and history of spontaneous abortion were collected. Anthropometric measurements including weight, height, body mass index (BMI), waist circumference (WC) (measurement of the circumference of the abdomen above the navel), hip circumference (HC) (measurement at the widest portion of the hip), and systolic and diastolic blood pressure in a sitting position after 10 minutes rest were measured. Presence of galactorrhea and acanthosis nigricans (grey-brown pigmentation with dryness and roughness of skin), and any type of menstrual disturbance (oligomenorrhea or amenorrhea) were evaluated by a gynecologist.

**Statistical analysis**

For the statistical analysis, SPSS software version 21.0 (SPSS, SPSS Inc., Chicago, IL, USA) was used. Quantitative data were shown as mean and standard deviation; also categorical data were shown as number (percentage). One-way analysis of variance (ANOVA) was used for comparison means among groups. Also, the least significant difference (LSD) post hoc test was used when ANOVA test results were significant. To compare frequencies among groups, the chi-square test was used, but when the frequencies were less than 5 in > 20% of the cells, the Fisher’s exact test was used. A P-value less than 0.05 was considered statistically significant.

**RESULTS**

**Prevalence of PCOS phenotypes**

Our study included 161 women with PCOS with a mean age of 25.63 ± 5.17. Most of the women (70.7%) were married and the rest were single. Most of the patients were categorized as IM + PCO + HA phenotype (54%), followed by IM + HA (28%), IM + PCO (13%), and PCO + HA (5%).

**Demographic characteristics and fertility features of the PCOS phenotypes**

There were no significant differences among the different phenotypes in terms of mean age (P = 0.114) and mean infertility duration in infertile women (P = 0.896). Using the Fisher’s exact test, there were no significant differences among the phenotypes in terms of marital status (P > 0.349), family history of diabetes (P > 0.094), history of infertility (P > 0.085), history of parity (P > 0.080), menstrual disturbance (P > 0.331), and history of spontaneous abortion (P > 0.127) (Table 1).

**Anthropometric features, ovarian volume and blood pressure**

There were no significant differences among the 4 phenotypes in terms of blood pressure and anthropometric measurements including weight, height, BMI, WC, HC, and waist/hip (W/H) ratio and among the groups. Mean ovarian volume in the IM + PCO + HA phenotype was significantly greater than the IM + HA (P = 0.0001) and PCO + HA (P = 0.008) groups. Mean ovarian volume in IM + HA phenotype was significantly smaller than the IM + PCO (P = 0.0001) and PCO + HA (P = 0.029) phenotypes (Table 2).

**Clinical features of the four PCOS phenotypes**

Prevalence of hirsutism in the IM + HA phenotype was higher than the other phenotypes. None of the women with IM + PCO phenotype had hirsutism. Difference in the prevalence of hirsutism among the

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### Table 1: Demographic characteristics, family history of diabetes and fertility features of PCOS women in different phenotypes

<table>
<thead>
<tr>
<th>Variables</th>
<th>IM + PCO + HA</th>
<th>IM + PCO</th>
<th>IM + HA</th>
<th>PCO + HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>26.16 ± 4.82</td>
<td>25 ± 4.79</td>
<td>26 ± 4.73</td>
<td>22.12 ± 2.10</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>18 (20.7)</td>
<td>4 (19)</td>
<td>6 (13.3)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Married</td>
<td>69 (79.3)</td>
<td>17 (81)</td>
<td>39 (86.7)</td>
<td>6 (73)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>33 (38.4)</td>
<td>9 (47.4)</td>
<td>24 (54.5)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>History of spontaneous abortion</td>
<td>6 (9)</td>
<td>1 (6.3)</td>
<td>4 (11.8)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>History of infertility</td>
<td>54 (78.3)</td>
<td>10 (58.8)</td>
<td>22 (56.4)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>Duration of infertility (months)</td>
<td>39.81 ± 46.73</td>
<td>38.20 ± 49.60</td>
<td>31.45 ± 25.78</td>
<td>35.75 ± 48.32</td>
</tr>
<tr>
<td>History of parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>11 (16.4)</td>
<td>2 (12.5)</td>
<td>11 (32.4)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>56 (83.6)</td>
<td>14 (87.5)</td>
<td>23 (67.6)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Menstrual disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>78 (89.7)</td>
<td>20 (95.2)</td>
<td>43 (95.6)</td>
<td>0</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>9 (10.3)</td>
<td>1 (4.8)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are shown as mean ± SD or number (percent)

IM: irregular menstruation; PCO: polycystic ovary; HA: hyperandrogenism
Table 2: Comparison of anthropometric features, ovarian volume and blood pressure of different PCOS phenotypes

<table>
<thead>
<tr>
<th>Variables</th>
<th>IM + PCO + HA</th>
<th>IM + PCO</th>
<th>IM + HA</th>
<th>PCO + HA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>71.69 ± 15.16</td>
<td>74.40 ± 15.93</td>
<td>72.98 ± 13.40</td>
<td>66.62 ± 17.78</td>
<td>0.616</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.54 ± 6.02</td>
<td>161 ± 6.10</td>
<td>159.62 ± 5.96</td>
<td>157.87 ± 4.76</td>
<td>0.613</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.15 ± 5.72</td>
<td>28.76 ± 6.12</td>
<td>28.68 ± 5.14</td>
<td>26.59 ± 6.36</td>
<td>0.770</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>87.98 ± 12.24</td>
<td>84.23 ± 13.41</td>
<td>86.74 ± 10.96</td>
<td>81.50 ± 8.91</td>
<td>0.364</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>106.17 ± 11.09</td>
<td>105.59 ± 11.30</td>
<td>107.40 ± 10.49</td>
<td>105.43 ± 11.69</td>
<td>0.911</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.83 ± 0.06</td>
<td>0.77 ± 0.08</td>
<td>0.81 ± 0.09</td>
<td>0.77 ± 0.03</td>
<td>0.145</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>110.13 ± 12.56</td>
<td>108.42 ± 12.59</td>
<td>108.84 ± 13.66</td>
<td>106.25 ± 9.16</td>
<td>0.817</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>68.86 ± 9.47</td>
<td>68.42 ± 10.15</td>
<td>67.44 ± 10.71</td>
<td>63.75 ± 9.16</td>
<td>0.531</td>
</tr>
<tr>
<td>Ovarian volume (cm²)</td>
<td>12.36 ± 3.18</td>
<td>11.54 ± 3.52</td>
<td>7.18 ± 1.29</td>
<td>9.56 ± 3.45</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Data are showed as mean ± SD

IM: irregular menstruation; PCO: polycystic ovary; HA: hyperandrogenism; BMI: body mass index; BP: blood pressure

Comparisons among groups were performed with the one way analysis of variance test.

Prevalence of alopecia in the IM + PCO + HA phenotype was significantly higher (46%). This prevalence in the IM + PCO phenotype was significantly lower than the IM + PCO + HA (P = 0.012) and IM + HA (P = 0.028) groups. Among the other phenotypes, there were no significant differences in terms of alopecia prevalence.

Prevalence of morphologic PCO was significantly different among the four PCOS phenotypes [IM + HA Vs IM + PCO + HA (P = 0.0001), IM + PCO (P = 0.0001), and PCO + HA (P = 0.0001)]. In other clinical features, there were no significant differences among the four phenotypes (P > 0.05) as shown in Table 3.

Biochemical features of the four PCOS phenotypes

Among the biochemical variables that were assessed, there were significant differences among the four phenotype groups in terms of mean levels of 17-OHP, LH, and ratio of LH/FSH. Mean level of 17-OHP was significantly lower in the IM + PCO phenotype assessed.

Table 3: Clinical features of the subjects in different PCOS phenotypes

<table>
<thead>
<tr>
<th>Variables</th>
<th>IM + PCO + HA</th>
<th>IM + PCO</th>
<th>IM + HA</th>
<th>PCO + HA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactorrhea</td>
<td>9 (10.3)</td>
<td>1 (4.8)</td>
<td>7 (15.6)</td>
<td>1 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>17 (19.5)</td>
<td>6 (28.6)</td>
<td>13 (28.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>43 (49.4)</td>
<td>7 (33.3)</td>
<td>24 (53.3)</td>
<td>2 (25)</td>
<td></td>
</tr>
<tr>
<td>Hirsutism</td>
<td>68 (78.2)</td>
<td>0</td>
<td>36 (80)</td>
<td>2 (25)</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>40 (46)</td>
<td>3 (14.3)</td>
<td>19 (42.2)</td>
<td>3 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Morphologic of PCO</td>
<td>74 (88.1)</td>
<td>20 (100)</td>
<td>0</td>
<td>7 (87.5)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are showed as number (percent).

IM: irregular menstruation; PCO: polycystic ovary; HA: hyperandrogenism

Table 4: Comparison of biochemical features among the different PCOS phenotypes

<table>
<thead>
<tr>
<th>Variables</th>
<th>IM + PCO + HA</th>
<th>IM + PCO</th>
<th>IM + HA</th>
<th>PCO + HA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>1.90 ± 2.14</td>
<td>1.35 ± 0.91</td>
<td>1.48 ± 0.78</td>
<td>1.34 ± 0.53</td>
<td>0.351</td>
</tr>
<tr>
<td>DHEAS (ng/ml)</td>
<td>224.92 ± 118.36</td>
<td>193.56 ± 79.21</td>
<td>258.09 ± 157.96</td>
<td>190.09 ± 56.75</td>
<td>0.180</td>
</tr>
<tr>
<td>17-OHP (ng/ml)</td>
<td>1.17 ± 0.68</td>
<td>0.69 ± 0.38</td>
<td>0.98 ± 0.59</td>
<td>1 ± 0.01</td>
<td>0.010</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>8.37 ± 4.81</td>
<td>7.38 ± 4.06</td>
<td>8.60 ± 5.46</td>
<td>10.63 ± 8.91</td>
<td>0.047</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>6.04 ± 2.03</td>
<td>6.45 ± 1.18</td>
<td>6.27 ± 1.63</td>
<td>6.25 ± 1.20</td>
<td>0.777</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>1.45 ± 0.70</td>
<td>1.21 ± 0.68</td>
<td>1.13 ± 0.46</td>
<td>1.69 ± 0.71</td>
<td>0.017</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>178.89 ± 35.17</td>
<td>183.71 ± 28.81</td>
<td>175.27 ± 36.31</td>
<td>166.75 ± 34.98</td>
<td>0.630</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>155.40 ± 79.70</td>
<td>145.76 ± 61.40</td>
<td>147.77 ± 98.91</td>
<td>132.13 ± 73.74</td>
<td>0.848</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>41.16 ± 8.07</td>
<td>41.30 ± 9.47</td>
<td>41.83 ± 9.20</td>
<td>42.30 ± 5.57</td>
<td>0.965</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>111.01 ± 30.65</td>
<td>114.99 ± 26.14</td>
<td>112.33 ± 30.35</td>
<td>102.84 ± 29.48</td>
<td>0.799</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>94.14 ± 20.52</td>
<td>90.80 ± 10.49</td>
<td>93.25 ± 22.38</td>
<td>90.75 ± 10.65</td>
<td>0.894</td>
</tr>
<tr>
<td>2 HPP (mg/dl)</td>
<td>118.07 ± 43.28</td>
<td>95.47 ± 19.38</td>
<td>110.77 ± 33.67</td>
<td>108 ± 28.31</td>
<td>0.149</td>
</tr>
<tr>
<td>AST</td>
<td>21.76 ± 9.23</td>
<td>24 ± 9.23</td>
<td>22.62 ± 14.49</td>
<td>17.63 ± 4.31</td>
<td>0.540</td>
</tr>
<tr>
<td>ALT</td>
<td>18.84 ± 10.09</td>
<td>22 ± 12.42</td>
<td>20.07 ± 14.99</td>
<td>14.88 ± 5.64</td>
<td>0.481</td>
</tr>
<tr>
<td>TSH</td>
<td>3.28 ± 3.64</td>
<td>2.13 ± 1.06</td>
<td>3.06 ± 3.09</td>
<td>3.61 ± 1.83</td>
<td>0.489</td>
</tr>
<tr>
<td>Prolactine</td>
<td>19 ± 10.13</td>
<td>15.29 ± 5.50</td>
<td>17.72 ± 11.42</td>
<td>18.99 ± 9.01</td>
<td>0.481</td>
</tr>
</tbody>
</table>

*Data are showed as mean ± SD

IM: irregular menstruation; PCO: polycystic ovary; HA: hyperandrogenism; DHES: dehydroepiandrosterone; 17-OHP: 17-hydroxyprogesterone; LH: luteinizing hormone; FSH: follicle stimulating hormone; TG: Triglyceride; HDL: high density lipid; LDL: low density lipid; FBS: Fasting blood sugar; 2HPP: 2-hour postprandial; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TSH: thyroid-stimulating hormone

Comparisons among groups were performed with the one way analysis of variance test.
than the IM + PCO + HA phenotype (p = 0.001). Mean level of LH was highest in the PCO + HA group. Mean LH level in the IM + HA phenotype was significantly lower than the IM + PCO + HA (p = 0.042) and PCO + HA (p = 0.017) groups. Women in the PCO + HA phenotype had the highest ratio of LH/FSH. This ratio in the IM + HA phenotype was significantly lower than the IM + PCO + HA (P = 0.007) and PCO + HA (P = 0.024) groups (Table 4).

**DISCUSSION**

Based on our findings, the majority of PCOS women were categorized into the IM + PCO + HA phenotype (54%), followed by IM + HA (28%), IM + PCO (13%), and PCO + HA (5%). Consistent with our finding, most of the studies in different regions of the world have reported a higher prevalence of the IM + PCO + HA phenotype than other phenotypes\[13-20\]. However, the prevalence of other phenotypes in our study was not similar to most of the previous studies and this may be due to ethnic and racial differences\[10\]. Distribution of the four phenotypes in our study is similar to Panidis et al’s study that was carried out in Greece. In that study, the prevalence of IM + PCO + HA, IM + HA, IM + PCO, and PCO + HA phenotypes were 48.2%, 30.7%, 11.4%, and 9.7%, respectively\[20\]. Also, PCOS phenotype prevalence in a study conducted on Kurdish women in Erbil were similar to our finding in that the prevalence of IM + PCO + HA, IM + HA, IM + PCO, PCO + HA were 42%, 24%, 20%, and 14%, respectively\[21\].

In another study, the prevalence of IM + PCO + HA was highest (45.5%), followed by IM + HA (40.2%), PCO + HA (7.4%), and then IM + PCO (6.9%)\[19\]. All of these studies were conducted in the Middle East and Mediterranean region. It is evident that there are similarities in PCOS presentation among women of the Middle Eastern and Mediterranean region\[10,12\]. In Pehlivanov and Orbetova’s study in Bulgaria, the prevalence of IM + PCO + HA was highest (58.6%) followed by PCO + HA (20%), IM + HA (11.4%), and IM + PCO (10%)\[19\]. Chae et al’s study was conducted on Korean women and the prevalence of IM + PCO + HA was the highest (52.4%), followed by IM + PCO (31.3%), IM + HA (13.9%) and PCO + HA (2.4%)\[13\]. In Welt et al’s study done in the USA, the prevalence of IM + PCO + HA was the highest (71.3%), followed by PCO + HA (18.4%), IM + PCO (8.6%), and then IM + HA (1.7%)\[16\]. However, in a study in Esfahan, Iran, it was shown that the prevalence of the IM + PCO phenotype was the highest (46.8%), followed by IM + PCO + HA (32.1%), IM + HA (14.8%), and then PCO + HA (4.3%)\[11\]. The highest prevalence of complete PCOS suggests that PCOS women present with the disease having most of the clinical features. In most studies, the PCO + HA phenotype had the lowest prevalence\[11,13,20,21\]. Women with PCO + HA phenotype might have less symptoms than the other phenotypes and this could reduce their attendance in gynecologic clinics.

In the present study, we did not find statistically significant differences in anthropometric measurements including weight, height, BMI, WC, HC, and W/H among the four phenotypes. In Panidis et al’s study that measured weight, BMI and W/H, only the difference in W/H between the IM + PCO + HA and PCO + HA groups was significant\[20\]. In Chae et al’s study, BMI was not different among the four phenotypes, but in the IM + PCO phenotype, WC and W/H were significantly lower than in the IM + PCO + HA or IM + HA groups\[13\]. In Chae et al’s study, the means of BMI among the four groups were similar, but WC between IM + PCO + HA and IM + PCO was significantly different\[13\]. Mehrabian et al reported that in the IM + HA group, the mean BMI was significantly higher than in the IM + PCO + HA and IM + PCO groups. Also weight, WC, and HC were significantly different among the four groups, but post hoc analyses were not performed in that study\[11\]. In Zhang et al’s study, BMI and W/H were significantly increased in women with IM + HA and IM + PCO + HA phenotypes compared with those with PCO + HA and IM + PCO + HA phenotypes\[22\]. In Thathapudi et al’s study, among the PCOS subgroups, women in the IM + PCO + HA phenotype had higher BMI, WC, and HC, but the W/H was similar in the PCOS subgroups\[21\].

Based on our study findings, prevalence of hirsutism in the IM + HA phenotype was the highest and none of the women in the IM + PCO phenotype had hirsutism. The prevalence of hirsutism in the IM + HA and IM + PCO + HA groups were significantly higher than in the other two phenotypes.

The free testosterone levels among the different PCOS phenotypes in our sample ranged from 0.20 - 8.57 and is shown as mean and standard deviation due to the need to report a defined number for each character to make a comparison among the four phenotypes (Table 4). Since the patients participating in this study referred to gynecologist clinics, and most of the patients with severe hirsutism commonly refer to dermatologist, it seems that the lower prevalence of clinical hyperandrogenism in this study can be justified.

Also, the prevalence of alopecia in the IM + PCO + HA phenotype was the highest. In Chae et al’s study, hirsutism in the IM + HA phenotype was more significantly severe than in the IM + PCO + HA phenotype\[13\]. In Thathapudi et al’s study, the IM + PCO + HA phenotype had more hirsutism (93%) compared to the PCO + HA group (82%) and alopecia was reported more in the IM + PCO + HA phenotype (68%) compared to the PCO + HA group (56.5%)\[12\].
Based on our findings among biochemical variables that were assessed, there were significant differences among the four phenotype groups in terms of mean level of 17-OHP, LH, and LH/FSH ratio. Level of 17-OHP was lowest in the IM + PCO + HA phenotype and highest in the IM + PCO + HA group. There was significant difference between IM + PCO + HA and IM + PCO + HA phenotype showed the lowest level of 17-OHP, but there was no significant difference between the IM + PCO + HA phenotype and PCO + HA phenotype. Consistent with our findings, in Panidis et al's study, the lowest and highest 17-OHP were reported in the IM + PCO and IM + PCO + HA groups, respectively and there was significant difference between the IM + PCO + HA and IM + PCO + HA groups. Also, in Welt et al's study, the level of 17-OHP was lowest in the IM + PCO phenotype.

The level of LH was highest in the PCO + HA group and there were significant differences between IM + HA and IM + PCO + HA as well as between IM + HA and PCO + HA. Women with the PCO + HA phenotype had the highest LH/FSH ratio and differences between the IM + HA and IM + PCO + HA groups; also IM + HA and PCO + HA groups were significant.

In Chae et al's study, there were no differences in the levels of LH, FSH and LH/FSH ratio among the PCOS phenotypes\[13\]. In Dewailly et al's study, women in IM + PCO + HA group had the highest level of LH and difference between IM + PCO + HA and IM + PCO; also IM + PCO + HA and PCO + HA were significant\[13\]. In Welt et al's study, the LH and LH/FSH ratio were higher in women with the IM + HA phenotype than in women with PCO + HA, but FSH levels did not differ among the phenotype groups\[16\]. In Zhang et al's study, the level of LH and the LH/FSH ratio were significantly lower in PCO + HA than the other phenotypes, but there were no significant differences among groups in terms of FSH levels\[22\].

The limitation of our study was related to sampling. We only recruited PCOS women who attended two private infertility clinics and a public endocrinology clinic in Rasht and that can limit the representativeness of our findings.

CONCLUSION

There were no significant differences in terms of anthropometric features among the four different phenotypes. Also, among the four phenotypes, prevalence of clinical features except prevalence of hirsutism, alopecia, and PCO were the same. In terms of biochemical features, differences among the four phenotypes were significant only in levels of 17-OHP and LH and ratio of LH/FSH. As a result of higher prevalence of clinical hyperandrogenism in HA+IM and HA+IM+PCOS phenotypes, which included hirsutism and acne compared to other phenotypes, they need more aggressive screening in specific disease and may induce long term morbidities such as infertility and cardiovascular complications.

The accurate diagnosis of PCOS has a major role in its clinical management. Although the overall findings show that most of the anthropometric, clinical and biochemical features were similar in women with different phenotypes of PCOS, further studies are needed to determine the clinical application of results for PCOS management and to determine features of PCOS in other ethnicities in Iran and other Asian countries.

ACKNOWLEDGMENT

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REFERENCES

The Relation between Serum Vitamin D Levels and Hashimoto Thyroiditis in Women

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ABSTRACT

Objective: Vitamin D has immunomodulatory effects which suggest a possible association between low serum 25-hydroxyvitamin D (25-OH D3) levels and autoimmune thyroid diseases. This study was conducted to investigate such a relation between low serum 25-OH D3 levels and Hashimoto thyroiditis (HT).

Design: Prospective, case-control study

Setting: Internal Medicine Clinic of Sakarya University, Turkey

Subjects: Serum 25-OH D3 levels were measured in 498 women presented to the outpatient clinic for routine history and physical examination. Thyroid hormones and antibodies were obtained in all patients. Thyroid ultrasonography was performed in antibody positive patients.

Intervention: Blood tests and neck ultrasound

Main outcome measures: Vitamin D levels in Hashimoto Thyroiditis

Results: Serum 25-OH D3 levels were significantly lower in patients with at least one thyroid antibody positive, compared to thyroid antibody negative patients (P = 0.013). Serum 25-OH D3 levels were also lower in anti-thyroglobine (TgAb) positive patients compared to antibody negative patients (P = 0.010). There was a statistically significant negative correlation between anti-TgAb and serum 25-OH D3 levels (P < 0.001). There was no statistically significant difference in serum 25-OH D3 levels between anti-thyroid peroxidase positive (TPOAb) patients and antibody negative patients (P = 0.643).

Conclusion: Women with HT thyroiditis have lower vitamin D levels compared to women without HT thyroiditis. We determined that serum 25-OH D3 insufficiency was 1.7 times more likely to be present in patients with HT. This insufficiency may increase the risk of HT disease.

INTRODUCTION

In recent years, studies reporting the increased risk in vitamin D deficiency and extra-medullary systemic diseases have increased. Especially, the relation between vitamin D deficiency and the autoimmune diseases that stem from it, as well as oncological diseases, diabetes mellitus, pregnancy and fetal development, mortality and spiritual health have been emphasized in recent studies[1].

Many authors accept that the patho-physiological mechanism of autoimmune thyroid disease (AITD) develops with the production of certain auto-antibodies that are reactive against thyroid antigens such as thyroid peroxidase and thyroglobulin. Genetic susceptibility and various environmental factors contribute towards AITD development[2]. Hashimoto Thyroiditis (HT) develops as a result of the reaction formed by the T and B-cells against thyroid antigens in patients with genetic susceptibility[3].

Vitamin D has immunomodulatory effects, besides its well-known role in calcium homeostasis. Active 1,25 (OH)2 D3 inhibits cellular differentiation, proliferation and apoptosis[4]. The latest data obtained in studies reveal the relation between vitamin D deficiency and autoimmune thyroid diseases[5]. Given these associations and high prevalence of HT in women, we planned to evaluate the relation between HT disease and 25-OH D3 in the female patients of our study.

SUBJECTS AND METHODS

Our study was conducted with 453 women in total. Of these, 253 patients were followed up for HT, and 200 people, who did not have any autoimmune
diseases, served as the control group. These patients were registered at Sakarya University School of Medicine Internal Medicine clinic from March 2013 to October 2013. The clinical and serologic data of the HT patients: the data on their ages, anti-thyroid peroxidase positive (TPOAb), anti-thyroglobine (TgAb), thyroid stimulant antibody (TSH) and B-mode ultrasonography reports were received from the patient files in a retrospective manner. Exclusion criteria were as follows: history of other autoimmune disease, pregnancy, vitamin D, immuno-suppressive drug use and being under the age of 18. Diagnosis of HT was made with overt clinical hypothyroidism, existence of diffused goiter in B-mode ultrasonography, TPOAb and/or TgAb positivity. The control group patients were selected with the criteria as follows: normal history and physical exam, normal basic metabolic panel and thyroid hormones, no previous diagnosis of thyroid disease or any other autoimmune diseases, having normal thyroid volume in B ultrasonography, and negative TPOAb and TgAb.

The following hormonal data were used in the study: serum TSH (reference range: 0.35 – 4.94 mIU/L), free T3 (FT3) (reference range: 2.63 – 5.70 pmol/L), free T4 (FT4) (reference range: 9.01 – 19.05 pmol/L), TgAb (cutoff level: 4.11 IU/mL) and TPOAb (cutoff level: 5.61 IU/mL), which were measured using automated immunochemiluminescent assay (ICMA) kits (Abbott, IL, USA). Serum 25-hydroxyvitamin (25-OH D3) levels were used to evaluate the vitamin D status, which were measured with Commercial Euglobulin Clot Lysis Assay (ECLA) Kit (Roche, Germany). According to Endocrine Association criteria, the following values were defined: 25-OH D3 levels were used to evaluate the vitamin D status, vitamin D insufficiency (< 20 ng/mL), deficient (21 - 29 ng/mL), and sufficient (≥ 30 ng/mL) [9]. We grouped patients with 25-OH D3 < 30 ng/mL as vitamin D deficient.

Statistics
Continuous variables are presented as means ± standard deviation for continuous and normally distributed variables and median (interquartile range) for the non-normally distributed variables. Student’s t-test and Mann-Whitney U test were used for comparison of mean values between the groups. Linear regression analysis was used to examine the relationship between log-transformed TgAb/TPOAb titer and TSH, 25-OH D3, and other biochemical variables. Multivariate regression analysis was performed to identify the predictive variables. Categorical associations were evaluated by using χ² test and multiple logistic regression. Goodness of fit was determined by using Nagelkerke R² and Hosmer-Lemeshow goodness-of-fit test. The level of significance was set at 0.05. All calculations were performed using the SPSS 10.0 for Windows (Chicago, IL, USA).

RESULTS
Four hundred and fifty-three female patients participated in the study (253 HT patients, 200 people control group, average age 40.3 ± 12.8 years). There were no differences between the patient and the healthy control group in terms of age (P = 0.589). Vitamin D deficiency was detected in 272 (60%) subjects. Vitamin D deficiency in HT patients was 59.1% (n = 161), and 40.8% (n = 111) in the control group. The clinic and laboratory characteristics of the patients are given in Table 1. The vitamin D deficiency frequency according to the existence of thyroid antibody is given in Table 2. Vitamin D deficiency was determined to be highest in the TgAb positive HT patients (66.2%, n = 145).

| Table 1: The characteristics of the patients and serum 25-OH-D3 levels |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Patient Characteristics     | Hashimoto Thyroiditis       | Control Group                | P-value                     |
| Age                         | 40.3 ± 12.8                 | 41.2 ± 12                    | 0.589                       |
| TPOAb (IU/mL)               | 130.2 ± 270                 | 2.4 ± 1.1                    | 0.000                       |
| TgAb (IU/mL)                | 76.7 ± 198.2                | 1.2 ± 1.3                    | 0.000                       |
| TSH (mIU/L)                 | 2.7 ± 3.9                   | 2.4 ± 5.1                    | 0.002                       |
| TPOAb and/or TgAb (n+, %)   | 253                         | 250                          |                             |
| 25 (OH) D3 (ng/mL)          | 33 ± 29.6                   | 43.7 ± 26.2                  | 0.001                       |
| Sufficiency (n, %)          | 92 (33.3)                   | 89 (45.5)                    | -                           |
| Insufficiency (n, %)        | 161 (63.6)                  | 111 (55.5)                   | -                           |
| Total                       | 253                         | 200                          |                             |
| TSH: thyroid-stimulating hormone; 25(OH) D3; serum 25-hydroxyvitamin D; TPOAb: anti-thyroid peroxidase antibody; TgAb: anti-thyroid-globulin antibody |

TSH levels were higher in the HT patients (TSH = 2.7 ± 3.9 mIU/L) compared to the control group (TSH = 2.4 ± 5.1 mIU/L) (P = 0.002). 25-OH D3 levels were lower in HT patients (25-OH D3 = 33 ± 29.6 ng/mL)

| Table 2: Vitamin D insufficiency prevalence according to thyroid antibody existence |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Patient Characteristics     | 25 (OH) D3<30 ng/mL         | 25 (OH) D3>30 ng/mL         | P-value                     |
| TPOAb (IU/mL) (n+, %)       | 102 (61.4)                  | 64 (38.5)                   | 0.589                       |
| TPOAb (IU/mL) (n-, %)       | 170 (59.2)                  | 117 (40.7)                  | 0.000                       |
| TgAb (IU/mL) (n+, %)        | 145 (66.2)                  | 74 (33.7)                   | 0.000                       |
| TgAb (IU/mL) (n-, %)        | 127 (54.2)                  | 107 (45.7)                  | 0.002                       |
| TPOAb and/or TgAb (n+, %)   | 161 (63.6)                  | 92 (36.4)                   | -                           |
| TPOAb and/or TgAb (n-, %)   | 111 (55.5)                  | 89 (45.5)                   | 0.001                       |
| Total                       | 253                         | 200                          |                             |
| TPOAb: Anti-thyroid peroxidase antibody; TgAb: anti-thyroid-globulin antibody; 25(OH) D3: serum 25-hydroxyvitamin D |
compared to the control group (25-OH D$_3$ = 43.7 ± 26.2 ng/mL) ($P = 0.001$). There were no associations between the serum 25-OH D$_3$ level, TPOAb, TSH in HT patients and control group patients. The 25-OH D$_3$ levels were lower in TgAb positive HT patients compared to the control group patients ($P = 0.010$) (Fig 1). There was a significant negative correlation between anti-TgAb levels and serum 25-OH D$_3$ levels (Spearman $r = -0.166$; $P < 0.001$). No association was found between TPOAb (+/-) and serum 25-OH-D$_3$ (insufficient/normal) in HT or the control group ($P = 0.643$ and $P = 0.690$, respectively). A significant association was found between TgAb (+/-) and serum 25-OH D$_3$ (insufficient/normal) categorical variables (Pearson $\chi^2$: 6.72, $P = 0.006$ and Pearson $\chi^2$: 3.082, $P = 0.079$, in HT patients and the control group, respectively). Vitamin D deficiency was 1.68 times more common in TgAb positive HT patients.

DISCUSSION

Vitamin D deficiency is a global health problem. High prevalence of vitamin D deficiency has been reported all over the world in the reports of studies from America, Australia, Africa and Asia$^6$. These situations have been explained by lifestyle, use of protective ointments, nutrition and somewhat with geographical conditions. Vitamin D deficiency (serum 25-OH D$_3$ levels < 30 ng/mL) was detected in 272 patients in our study. The highest vitamin D deficiency prevalence was detected in TgAb positive HT patients ($n = 145$, 66.2%) and this finding agrees with the literature$^7$. The association between TgAb positivity and HT was significant. Moreover, we found a significant negative correlation between TgAb levels and serum 25-OH D$_3$. On the other hand, vitamin D deficiency prevalence in TPOAb positive HT patients was similar to the healthy control group.

Recent studies report that there might be a relation between the vitamin D deficiency prevalence being high in HT patients$^8$$^{10}$. Our study findings of lower levels of 25-OH D$_3$ in HT patients agree with these reports. It was also found that 25-OH D$_3$ levels were at much lower levels in patients with autoimmune diseases when compared with healthy control groups$^9$$^{10}$. In a meta-analysis released on AITD and vitamin D receptor gene polymorphisms, a significant relation was detected between vitamin D receptor gene polymorphism and autoimmune thyroid diseases$^{11}$. In our study, we detected that the serum 25-OH D$_3$ levels in HT patients were lower than the healthy control group ($P = 0.001$). It is possible that vitamin D deficiency plays a role in the pathological process of development of HT disease.

Similarly, vitamin D plays an important role in the regulation of T helper cell type 1 (Th1), Th2 and Th17 cells, and in the regulation of IFN-$\gamma$, IL-4, IL-17 secretion with its immunomodulator influence. These findings are consistent with our study and might explain our hypothesis that vitamin D deficiency contributes to the development of auto immune thyroid disease$^{12}$$^{14}$. Our findings also agree with several studies that reported 25-OH D$_3$ < 20 ng/mL to be a risk factor for positive thyroid autoantibodies (TPOAb, TgAb)$^{14}$$^{16}$. Finally, we also showed that there was 1.68-fold more vitamin D deficiency in TgAb positive HT women patients.

CONCLUSION

Vitamin D deficiency was higher in TgAb positive women compared to healthy female subjects. TgAb positive women were 1.7 times as likely to have vitamin D deficiency compared to TgAb negative healthy subjects. There was a significant negative correlation between TgAb levels and serum 25-OH D$_3$. These findings suggest that AITD may develop due to possible interaction between vitamin D and X chromosome. This interaction may explain the possible role of vitamin D in HT immunologic pathogenesis.

REFERENCES


Evidence Based Medicine and Guidelines: Awareness, Perceptions and Practice of Physicians from a University Hospital and Primary Health Care Centers, Jeddah, Saudi Arabia

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ABSTRACT

Objective: To assess the level of awareness, perceptions and practices of Jeddah’s physicians towards Evidence Based Medicine (EBM), and Evidence Based Practice Guidelines (EBPGs).

Design: A cross-sectional study was done.

Setting: Selected Primary Health Care Centers (PHCCs), and outpatient clinics from King Abdulaziz University Hospital (KAUH)

Subjects: A sample of 260 physicians working at the chosen facilities

Intervention(s): Physicians were selected through stratified random sample method. A standardized, anonymous, self-administered questionnaire was used. Visual Analogue Scales were utilized to rate physicians’ perceptions towards EBM. Descriptive and inferential statistics were done.

Main outcome measure(s): Identifying awareness, perceptions and practices of physicians towards EBM and EBPGs.

Results: Only less than one-third of the physicians reported that they can understand and explain EBM terms such as relative risk (29.6%), absolute risk (28.1%) and meta-analysis (28.5%). Most of the participants welcomed applying EBM in their practice. EBPG was reported as the most commonly used method for moving from opinion-based practice to EBM. Lack of training (86.2%) and internet accessibility (71.5%) hindered EBM application in practice. No statistical associations were found between both genders concerning their perceptions towards EBM. Physicians from KAUH had significantly better perception than PHCCs physicians (p < 0.01) regarding the opinion that “adoption of EBM placed a burden on their already overloaded schedules”. Concerning practice, 41.5% of the physicians did not perform any search influenced by their practice during the preceding year.

Conclusion: Physicians had good perceptions towards EBM, but their awareness and practices need improvement. EBM training programs and increased workplace internet accessibility are required.

INTRODUCTION

Evidence Based Medicine (EBM) deals with the use of the best available evidence for making sound decisions regarding patients’ care[1]. The concept of EBM initially commenced from Canada during the late 1990’s as a novel paradigm shift in medical practice and education[1,2].

EBM has rapidly gained international recognition and its scope has been broadened to involve nearly every health care profession. The importance of EBM increases in clinical practice, and physicians are being encouraged to improve their clinical care by applying EBM and Evidence Based Practice Guidelines (EBPGs)[3]. The grade of evidence is an essential constituent of EBM. Nowadays, there are a rising number of health organizations which use and improve the standards for developing clinical practice guidelines. EBM was given great consideration when doing the grades of guideline and recommendations[4]. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) presents a systematic and transparent direction to

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Physicians may make several clinical judgments every year regarding patients’ diagnosis, prognosis and management. Nevertheless, it is not easy to determine which of their decisions are in line with the best existing evidence and guidelines. Nowadays, knowledge about EBM and guidelines is a core competence in medical education. EBM remains a hot issue among health care providers. Meanwhile, physicians’ knowledge, perceptions and practices of EBM varies widely. A study from the United Kingdom reported that health professionals supported the incorporation of Evidence-Based Practice (EBP) into their continuous management. Nevertheless, it is not easy to determine every year regarding patients’ diagnosis, prognosis and improve patients’ care.

In Jeddah, there is a paucity of published studies on physicians’ awareness, perceptions and practice towards EBM and EBPGs. Furthermore, to the best of our knowledge, there are no existing studies for a comparison between perceptions of physicians working in Primary Health Care Centers (PHCCs) and those working in the main Jeddah University regarding EBM and the guidelines. EBM needs to be applied to improve clinical practices. Therefore, this study was undertaken to assess the level of awareness, perceptions and practices of physicians working at Primary Health Care Centers and King Abdulaziz University Hospital (KAUH) towards EBM and EBPG in Jeddah, Saudi Arabia.

SUBJECTS AND METHODS

Ethical statement

The study conformed to the ethical standards of the Helsinki Declaration. Ethical approval was obtained from the Institutional Review Board (IRB) of KAUH with Reference Number 951-12. Administrative approval was also taken from the Jeddah Directorate of Health Affairs. In addition, a written informed consent was obtained from each participant.

A cross-sectional study was conducted in Jeddah during 2014. A stratified random sample method was used. Stratification took into consideration the district of the PHCCs, hence 5 randomly selected PHCCs were taken (one from each of the 5 Jeddah health districts). Concerning KAUH, stratification took in consideration the type of outpatient clinics.

For this study, a sample size of 260 physicians was needed to achieve 90% power to detect a difference (P̂1−P̂2) of 0.1 using a two-sided exact test with a significance level (alpha) of 0.05. We assumed that the population proportion of physicians who would have had inadequate awareness, perceptions and practice towards EBM and EBPGs under the null hypothesis (P̂0) is 0.5.

The stratification was done using the proportional allocation technique according to size of sample in the different strata (from KAUH and the PHCCs). All available physicians on the day of interview who accepted to participate in this study were recruited.

A standardized, confidential, self-administered questionnaire was utilized. The questionnaire was adapted by McColl et al. Face and content validity were assessed by two epidemiologists, and internal consistency reliability was assessed by Cronbach’s alpha test and was found to be 0.85.

The questionnaire contained close ended-questions for evaluating physicians’ awareness about EBM and EBPGs. It asked about EBM technical terms such as relative risk (RR), odds ratio (OR), absolute risk, systematic review, meta-analysis, clinical effectiveness, and number needed to treat (NNT), etc. They were also asked about journal extraction, publication reviews, and EBPG-specific databases.

Physicians were also asked about their perceptions regarding the methods used to move from opinion based practice towards EBM. The inquired methods were learning the skills of EBM, seeking and applying EBM summaries, and using EBPGs.

Visual analogue scales (VASs) were used to rate the physicians’ perceptions towards different EBM statements. Two statements rated perceptions of participants and their colleagues towards the current promotion of EBM. Other statements inquired about participants’ attitudes towards the usefulness of research findings in their patient management, percentage of their clinical practice which was evidence-based, and if practicing EBM improves patient care.

Negative physicians’ attitude towards EBM were also assessed by rating statements such as: EBM is of limited value in general practice as much of primary care lacks a scientific base, and that adoption of EBM places another demand on the already overloaded schedule of the physicians.

The questionnaire also included a free text section that permitted physicians to describe their views on the most important barriers that hinder the application of EBM during their practice.

Experiences and practices of the physicians regarding EBM were determined by asking if they had received any EBM courses or training at their workplace. Their application of EBM and EBPGs during their medical practice was also determined.

Data analysis

The data was analyzed using SPSS 20 (IBM SPSS Statistics 20, IBM Corporation, Armonk, NY, USA,
Descriptive statistics including frequencies (%), medians, means and standard deviations were computed. Non-parametric Mann-Whitney U test was conducted to compare the median perceptions’ scores of male and female physicians from KAUH and from PHCCs. Box plots were used to compare between two different distributions. All p-values < 0.05 were considered statistically significant.

RESULTS

A total of 260 (97.3%) physicians accepted to participate in the study. Their ages ranged from 24 - 56 years with a mean (SD) of 31.7 (7.2) years. The male to female ratio was 1:1.3.

Table 1 shows that physicians working at PHCCs represented 60% of the sample. Four-fifths of the participants were Saudis, and about three-fourths of them (74%) worked in urban areas. General practitioners (GPs) represented 69.2% of the sample.

Table 2 reveals that less than one-third of the physicians reported their ability to understand and explain EBM terms such as RR (29.6%), absolute risk (28.1%), OR (22.3%) and meta-analysis (28.5%). Furthermore, only about one-eighth of the participants reported that they could explain clinical effectiveness (11.9%), NNT (13.8%), confidence interval (13.8%) and heterogeneity (10%).
Fig 1 demonstrates that male physicians were slightly more welcoming to the current promotion of EBM compared to females (sentence A). In addition, equal proportions of both genders perceived that their colleagues were welcoming current EBM promotion (B), and that practicing EBM improves patient care (E). A higher proportion of females (compared to males) perceived that EBM was of limited value in general practice due to lack of a scientific base (F), and that adoption of EBM places additional demands on their already overloaded schedules (G). No statistical significant differences (P > 0.05) were found between both genders regarding their perception towards all EBM statements.

Fig 2 illustrates comparisons between the perceptions of physicians from PHCCs and KAUH

<table>
<thead>
<tr>
<th>Term</th>
<th>It would not be helpful for me to understand n (%)</th>
<th>Don’t understand but would like to n (%)</th>
<th>Some understanding n (%)</th>
<th>Understand and could explain to others n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk</td>
<td>7 (2.7)</td>
<td>68 (26.2)</td>
<td>108 (41.5)</td>
<td>77 (29.6)</td>
</tr>
<tr>
<td>Absolute risk</td>
<td>7 (2.7)</td>
<td>73 (28.1)</td>
<td>107 (41.2)</td>
<td>73 (28.1)</td>
</tr>
<tr>
<td>Systemic review</td>
<td>4 (1.5)</td>
<td>74 (28.5)</td>
<td>91 (35)</td>
<td>91 (35)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>8 (3.1)</td>
<td>109 (41.3)</td>
<td>85 (32.7)</td>
<td>58 (22.3)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>10 (3.8)</td>
<td>89 (34.2)</td>
<td>87 (33.5)</td>
<td>74 (29.5)</td>
</tr>
<tr>
<td>Clinical effectiveness</td>
<td>9 (3.5)</td>
<td>129 (49.6)</td>
<td>91 (35)</td>
<td>31 (11.9)</td>
</tr>
<tr>
<td>Number needed to treat</td>
<td>8 (3.1)</td>
<td>143 (55)</td>
<td>73 (28.1)</td>
<td>36 (13.8)</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>11 (4.2)</td>
<td>151 (58.1)</td>
<td>62 (23.8)</td>
<td>36 (13.8)</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>18 (6.9)</td>
<td>151 (58.1)</td>
<td>65 (25)</td>
<td>26 (10)</td>
</tr>
</tbody>
</table>

Table 2: General physicians’ understanding of the technical terms used in evidence based medicine

All p-values > 0.05 except statement G (p < 0.01)

Fig 2: Attitudes of physicians towards Evidence Based Medicine according to their place of work (primary health care center or King Abdulaziz University Hospital)

A: Attitude towards the current promotion of EBM
B: Attitude of most of your GP colleagues towards EBM
C: How useful are research findings in your day-to-day management of patients
D: Percentage of my clinical practice do you feel is currently evidence-based
E: Practicing evidence-based medicine improves patient care
F: EBM is of limited value in general practice because much of primary care lacks a scientific base
G: The adoption of EBM places another demand on already overloaded GPs
regarding EBM. Physicians from the university were more welcoming to the current promotion of EBM (A), and more in agreement that practicing EBM improves patients care (E) compared to their colleagues from PHCCs. On the other hand, a higher percentage of physicians from PHCCs (than KAUH physicians) thought that EBM was of limited value in general practice (F). No statistical significant differences were found between the perception of physicians from PHCCs and KAUH regarding most of the EBM statements. On the other hand, physicians from the university had significantly (p < 0.01) better attitudes (agreed less) regarding the adoption of EBM placing additional demands on their already overloaded schedules.

Table 3 reveals that EBPGs were reported as the most common (72.3%) method used by the physicians to move from opinion-based practice to EBM. They also perceived using EBPGs as the most appropriate (51.2%) method to apply in general practice. Furthermore, 63.9% of them believed that EBPGs could facilitate EBM practice. On the other hand, 42.7% perceived learning the skills of EBM as the method they were interested in using in the future.

Table 4 shows that 44.6% and 68.1% of the physicians reported receiving EBM course and/or training program at their workplace, respectively. Furthermore, only 34.6% of them reported having the possibility for extracting data from journals, reviewing publications, or databases relevant to EBM. The most frequently reviewed journals were the New England Journal of Medicine (NEJM), the British Medical Journal (BMJ), and American Academy of Family Physicians (AAFP). The Journal of the American Congress of Obstetricians and Gynecologists (ACOG) was reviewed only by 5% of the respondents.

It was found that during the one year prior to conducting the study, 37.3% of physicians did not perform any search on Medline or other bibliographic databases or have someone else do it on their behalf. The median number of performed searches on Medline (among those who did this search) was 10 times. Furthermore, 41.5% of them did not perform any search that was influenced by their practice. Among the rest of the physicians, the median times of access to Medline as an influence on practice were 4.1 times. It was found that 73.1% of the physicians reported that they accessed Medline from their homes. From the opinions of physicians, the most common factors that hindered the physicians from applying EBM in general practice are the lack of training (86.2%), lack of internet access (71.5%), rejection by members of the community (32.3%) and rejection of the physicians (31.1%).

### DISCUSSION

Only less than one-third of the physicians in the current study reported that they understood and could explain the terms related to EBM. This agrees with a recent Turkish study, where most of their physicians lacked knowledge about EBM[^13].

Concerning perceptions, most of our participants agreed that patients’ care can be improved by practicing EBM and this agrees with the results from many other studies[^6,14,13]. In the present study, male
physicians were slightly more welcoming to the current promotion of EBM compared to females. Furthermore, a higher percentage of female respondents thought that the adoption of EBM placed additional demands on their already overloaded schedules. However, another study done in the USA reported that females were more open to adopting evidence-based practices (EBPs)\textsuperscript{[10]}. This difference may be due to other loads placed on the female physicians from Saudi Arabia, or due to cultural differences between both countries.

Our results showed that physicians from the University Hospital were more welcoming to apply EBM than those from PHCCs. Similarly, a Jordanian study reported that more than half of the family physicians thought that EBM was of limited value in the primary care setting; as in a busy PHCC setting, critical appraisal is often neglected due to lack of knowledge or time constraints\textsuperscript{[6]}. Use of EBPGs was reported as the most frequently utilized method by physicians in our study to move from the opinion-based to EBM. However, it was reported from the Jordanian study that about half of their physicians viewed that searching and applying EBM summaries is the most commonly used method\textsuperscript{[6]}. This may be due to the lack of EBPGs for their physicians.

Our results revealed that during the year preceding the study, 37.3% of the physicians did not perform any internet search to influence their clinical practice, which agrees with a Belgium study\textsuperscript{[15]}. Some personal, organizational, and patient-related factors had been reported to hinder the application of EBM in practice\textsuperscript{[17,18]}. The most common factors that hindered physicians from applying EBM in the current study were lack of training and internet accessibility, and rejection by physicians and members of the community. Similarly, lack of time and unavailability of EBM resources have been cited from a survey conducted at Dubai PHCCs\textsuperscript{[18]}. The study of Abha found that physicians did not apply EBM in practice primarily due to lack of time and no access to the internet at work\textsuperscript{[10]}.

In the current study, about one-third of the physicians reported having the possibility to extract data from journals or review published works or databases relevant to EBM. An older study done in the UK in 1998, showed that physicians had little awareness about extracting journals, review publications, and databases which may be attributed to the time of conduction of their study\textsuperscript{[6]}.  

CONCLUSION

Most of the physicians had positive perceptions toward EBM and EBPGs, but they had some lack of knowledge and practices about them. Male physicians working at the University Hospital had slightly better perceptions towards EBM compared to others. Improvement in physicians’ awareness and practice regarding EBM and EBPGs is required through conduction of educational training programs (either directly or through e-learning). Public health officials need to promote more effective education and training to persuade physicians who are reluctant to adopt EBM practice and members of the community about the importance of application of EBM and EBPGs in clinical practice. Availability of high quality internet access is needed in all PHCCs and outpatient clinics for enhancing the application of EBM in clinical practices. Efforts should also be made for improving physicians access to different electronic databases by providing free access to them.

ACKNOWLEDGMENT

The authors would like to thank the physicians and participants in the study, and administrators who facilitated it. Special thanks to Laila Al-Nouri, Maha Behairi and Alaa Al-Ahdal for their help in data collection.

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REFERENCES


A Comparison of Functional Outcomes and Complications of Stapedotomy with and without Vein Graft Interposition in Patients with Otosclerosis

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ABSTRACT

Objective: To compare the functional outcomes and complications of stapedotomy with and without vein graft interposition

Design: Retrospective case study

Setting: Tertiary referral hospital

Subjects: Sixty otosclerosis patients (66 ears) that underwent primary stapedotomy surgery and followed up for at least 6 months

Interventions: Stapedotomy with vein graft interposition (n = 36) versus stapedotomy without interposition (n = 30)

Main outcome measures: Mean postoperative 4-frequency (500Hz, 1000Hz, 2000Hz, 4000Hz) air-bone gap, postoperative hearing gains for individual frequencies, sensorineural hearing loss and vertigo

Results: The mean postoperative 4-frequency (500Hz, 1000Hz, 2000Hz, 4000Hz) air-bone gap with interposition was significantly higher than without interposition (16.4 ± 9.4 dB versus 10.7 ± 7.4 dB, respectively). Analyses of postoperative hearing gains revealed higher gains without interposition in all frequencies, significant for frequencies at 500Hz and 1000Hz in AC, and 4000 Hz in BC thresholds. Although the frequency of sensorineural hearing loss and vertigo did not differ between groups, sensorineural hearing loss tended to be higher with vein graft interposition.

Conclusion: Stapedotomy without interposition required less manipulation, thereby leading to satisfactory results without major complications. Difficulties in performing the vein graft interposition technique requiring more manipulations and skill may be a disadvantage. Prospective randomized studies with larger series comparing different techniques can better evaluate the results.

INTRODUCTION

Otosclerosis is a localized disorder of bone metabolism of the otic capsule in which enchondral bone is restructured with disordered resorption and deposition of bone. It was first described by Antonio Valsalva in 1704 during an autopsy of a deaf individual, and the anatomic and pathologic characteristics of the disease were established by Rudolf Virchow in 1853. Adam Politzer was the first to use the term “otosclerosis” in 1912[1].

The first stapedectomy was performed by John Shea in 1956, and J.R. Causse used a teflon piston against vein graft sealing and described the interposition technique in 1963. In 1965, the small fenestra stapedotomy technique was reported by J. Marquet with the insertion of teflon prosthesis without interposition[2,3]. Through the years, the technique altered from stapedectomy to stapedotomy[4].

Today, many otologists prefer stapedotomy with interposition for the treatment of otosclerosis. Once in a while, one may question whether sealing is always necessary to achieve successful hearing results in stapes surgery. Recent studies report postoperative air-bone gaps (postABG) close to 10 dB or less in 94.2% otosclerosis patients with vein interposition[5], as compared to 81.8% without interposition[6]. Recently, a study compared the results of two different centers in a single study. The three month success rate was reported as 72.1% without interposition, compared to 93.2% with vein graft interposition[7].
In our clinic, both techniques are used by different surgeons. Since no publication exists that compares results within the same clinic; in this study, we aimed to compare the functional outcomes and complications of the stapedotomy with and without vein graft interposition performed within our clinic.

SUBJECTS AND METHODS

Stapes surgery was performed to 87 ears in 76 otosclerosis patients (11 bilateral cases) mostly by the two senior authors who are experts in ear surgery between 1997 and 2004 in Izmir Ataturk Research and Training Hospital, Department of Otorhinolaryngology. Female to male ratio was 3:5. The age of the 87 cases ranged between 17 – 57 years, and the mean was 40.4 years.

Sixty-eight ears of 62 patients who were followed-up for 6 months or longer were included in the study. The diagnosis of otosclerosis was based on clinical history of progressive hearing loss, normal otoscopic findings, negative Rinne test, audiogram showing a conductive hearing loss of at least 30 dB with the absence of stapedial reflex and findings compatible with otosclerosis during surgery. All cases included underwent primary stapes surgery. Cases with conductive hearing loss that were diagnosed as having tympanosclerosis, bone discontinuity or congenital anomalies during surgery and revision otosclerosis cases were excluded.

The medical records, including the preoperative history and audiometric measurements of the patients, were reviewed. All patients were asked to visit the outpatient clinic for otomicroscopic examination and audiologic measurements. Their history including family history, hormonal history, preoperative and postoperative presence of vertigo or tinnitus, presence of postoperative loud noise intolerance, taste disturbances and use of hearing aid postoperatively was obtained, and their informed consents were taken. The study was approved by Izmir Katip Celebi University Institutional Review Board.

Surgical techniques: A transcanal approach through an ear speculum was used. After, the crural arch was fractured and deposition into the hypotympanium, the footplate was perforated with a perforator, and a 0.6 mm teflon piston prosthesis trimmed to the desired length was placed in most of the cases. A 0.4 mm teflon piston was only used when there were anatomic difficulties. In the first group, an approximately 0.8 mm stapedotomy hole was made with a pick on the footplate and the prosthesis was placed without any sealing material. The stapedial tendon was left intact in both groups. In all of the cases, the surgery was performed under local anesthesia. All patients received postoperative antibiotics, and vestibulosuppressants were supplied if necessary.

Evaluation of Audiometric Results: The preoperative and short-term postoperative (between 1st and 6th month postoperative) audiologic measurements were reviewed from the medical records. The patients were asked to visit the clinic and their latest postoperative pure tone audiometric results were obtained. Audiologic evaluations were performed using an interacoustics AC30 clinical audiometer. Air conduction (AC) thresholds were obtained from 250 to 8000 Hz, and bone conduction (BC) thresholds were obtained from 500 to 4000 Hz.

Only AC and BC thresholds that were obtained at the same time postoperatively were used for calculation of ABG. We used a 4-frequency pure tone average (PTA) for AC and BC thresholds (0.5, 1, 2, and 4 kHz) according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO HNS) guidelines, except for thresholds at 3 kHz, which were substituted in all cases with those at 4 kHz. A postABG of 10dB or less was considered successful.

Comparisons of postoperative gain for the two groups were also performed in all frequencies for AC (250, 500, 1000, 2000, 4000, 8000 Hz) and BC (500, 1000, 2000, 4000 Hz) thresholds. A high frequency PTA of 1000, 2000, 4000 Hz was computed from preoperative and postoperative BC thresholds to evaluate sensorineural hearing loss (SNHL). BC thresholds at 4000 Hz were also compared separately to evaluate SNHL. A postoperative BC threshold that was 10 dB worse than the preoperative value was defined as SNHL.

Statistical analyses

Results were analyzed using descriptive statistics. Chi-square test was used for categorical data, and independent sample t-tests were used to test differences between groups for continuous variables. Correlation analyses were undertaken for preoperative and postoperative symptoms. All analyses were performed by running SPSS 15.0 software. Criterion for statistical significance was set at p < 0.05.

RESULTS

Among 68 operated ears followed-up for at least six months, postoperative SNHL developed in two patients (2.9%). One was severe (AC threshold between 60 - 80 dB) and one was total (AC threshold > 80 dB).
One of these surgeries was with vein interposition, while the other was without interposition. The records of these surgeries were not included in statistical analysis.

Overall, 66 ears were included in statistical analysis. The mean follow-up period was 29.5 months, ranging between 6 - 96 months.

Preoperative patient characteristics: Among the 66 ears included in the statistical analysis, 36 (54.5%) of them had undergone stapedotomy with vein interposition and are referred to as Group A throughout the manuscript. The remaining 30 cases (45.5%) without interposition are referred to as Group B. There was no difference regarding the distribution of sex, age and duration of the hearing loss before the surgery between the two groups (Table 1) (p > 0.05).

The mean 4-frequency preoperative ABG of 66 cases was 35.3 dB. The mean preoperative ABG values for the two groups are shown in Table 1. There was no statistical difference in preoperative ABG and preoperative AC and BC thresholds between groups. Preoperative comparison of AC and BC thresholds individually for 500, 1000, 2000, 4000 Hz also revealed no statistical difference between the two groups (Independent sample test, p > 0.05).

PostABG: The mean postoperative 4-frequency ABG of 66 cases was 13.8 ± 8.9 dB, and the overall success rate was 47% (31 ears). In 77.3% of the cases (51 ears), the postABG was ≤ 20 dB. The success rate was significantly higher (30.6% vs. 66.7%), and the postABG was significantly lower (16.4 ± 9.4dB vs. 10.7 ± 7.4dB) in Group B (Chi-square test, independent sample test p < 0.05) (Table 2). The distribution of postABG is shown in Fig 1. An improvement in postoperative BC of ≥ 10 dB was defined as overclosure. Overclosure was observed in 9 cases (25%) in Group A, and in 11 cases (36.7%) in Group B. The success rates were also compared at individual frequencies, and were significantly higher for all frequencies in Group B (Chi-Square test, p < 0.05) (Table 3). The mean

<table>
<thead>
<tr>
<th>Variables</th>
<th>With vein graft (n = 36)</th>
<th>Without vein graft (n = 30)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/Male ratio</td>
<td>25/11</td>
<td>23/7</td>
<td>NS*</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>40.3 ± 9.1</td>
<td>39.3 ± 8.4</td>
<td>NS*</td>
</tr>
<tr>
<td>Duration of hearing loss (years)</td>
<td>6.8 ± 5.6</td>
<td>7 ± 6</td>
<td>NS**</td>
</tr>
<tr>
<td>Mean preoperative ABG</td>
<td>36.3 ± 11.2 dB</td>
<td>34.2 ± 10.9 dB</td>
<td>NS**</td>
</tr>
<tr>
<td>Mean preoperative AC threshold</td>
<td>61.6 ± 13.5 dB</td>
<td>60 ± 15 dB</td>
<td>NS**</td>
</tr>
<tr>
<td>Mean preoperative BC threshold</td>
<td>25.4 ± 10.9 dB</td>
<td>25.8 ± 9.1 dB</td>
<td>NS**</td>
</tr>
</tbody>
</table>

Means were calculated with 0.5, 1, 2, and 4 kHz.
ABG: air-bone gap; AC: air conduction; BC: bone conduction; dB: decibel; NS: nonsignificant
*Chi-square test, p < 0.05, statistically significant
**Independent sample test, p < 0.05, statistically significant

Fig 1: The distribution of postoperative air-bone gaps (ABG)
postABG was higher for all frequencies in Group A and this was statistically significant at frequencies 500 and 2000 Hz (independent sample test, p < 0.05) (Table 3).

**Postoperative PTA thresholds:** The overall mean postoperative AC and BC thresholds were 35.1 ± 16.8 dB and 21.3 ± 10.9 dB, respectively. The mean postoperative AC threshold in Group B (29.3 ± 13 dB) was significantly lower than the threshold in Group A (40.0 ± 18.2 dB) (independent sample test, p = 0.034). There was no significant difference in the mean postoperative BC thresholds in groups (independent sample test, p > 0.05) (Table 2). Postoperative gains in Group A were lower in all AC and BC thresholds compared to Group B (Table 4). Vein graft interposition revealed a significantly lower gain at frequencies 500 Hz and 1000 Hz for AC and at 4000Hz for BC (independent sample test, p > 0.05).

**Audiometric evaluation of SNHL:** In Group A, 5 cases (13.9%) had high frequency SNHL (PTA at 1000, 2000, 4000 Hz more than 10 dB), while in Group B, none of the cases had SNHL. The difference was not significant (Chi-Square test, p > 0.05). Comparison of BC thresholds of Group A and B at 4000 Hz showed a higher percentage of SNHL in Group A (16.7% and 10%, respectively), but the difference was insignificant (Chi-Square test, p > 0.05).

**Preoperative and postoperative history and symptoms:** Fourteen patients in Group A and 7 patients in Group B had preoperative vertigo. Nine of the vertigo cases recovered postoperatively (6 in Group A and 3 in Group B), while in 11 cases, vertigo worsened postoperatively (5 in Group A and 6 in Group B). Twelve patients suffering from long-term postoperative vertigo were in Group A, and 9 were in Group B. Overall, 53 patients had preoperative vertigo. Thirty-five (66%) of the tinnitus cases reported an improvement or eradication of tinnitus postoperatively (16 in group A and 19 in group B).

---

**Table 2:** Comparison of Postoperative ABG, Success rate, AC and BC thresholds

<table>
<thead>
<tr>
<th>Variables</th>
<th>All cases</th>
<th>With vein graft (n = 36)</th>
<th>Without vein graft (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean postoperative ABG ± SD</td>
<td>13.8 ± 8.9 dB</td>
<td>16.4 ± 9.4 dB</td>
<td>10.7 ± 7.4 dB</td>
<td>0.031**</td>
</tr>
<tr>
<td>Success rate (ABG ≤ 10 dB)</td>
<td>47%</td>
<td>30.6%</td>
<td>66.7%</td>
<td>0.007**</td>
</tr>
<tr>
<td>Mean postoperative AC threshold ± SD</td>
<td>35.1 ± 16.8 dB</td>
<td>40.0 ± 18.2 dB</td>
<td>29.3 ± 13 dB</td>
<td>0.034**</td>
</tr>
<tr>
<td>Mean postoperative BC threshold ± SD</td>
<td>21.3 ± 10.9 dB</td>
<td>23.6 ± 11.7 dB</td>
<td>18.6 ± 9.3 dB</td>
<td>NS**</td>
</tr>
</tbody>
</table>

Means were calculated with 0.5, 1, 2, and 4 kHz
ABG: air-bone gap; AC: air conduction; BC: bone conduction; dB: decibel; NS: nonsignificant
*Chi-square test, p < 0.05, statistically significant
**Independent sample test, p < 0.05, statistically significant

**Table 3:** Comparison of success rates and mean ABG at individual frequencies

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>No of patients (Success Rate %)</th>
<th>Mean ± SD (dB)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With Vein graft</td>
<td>Without Vein graft</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>12 (33.3)</td>
<td>19 (63.3)</td>
<td>0.015*</td>
</tr>
<tr>
<td>1000</td>
<td>14 (38.9)</td>
<td>21 (70)</td>
<td>0.012*</td>
</tr>
<tr>
<td>2000</td>
<td>20 (55.6)</td>
<td>27 (90)</td>
<td>0.002*</td>
</tr>
<tr>
<td>4000</td>
<td>17 (47.2)</td>
<td>23 (76.7)</td>
<td>0.015*</td>
</tr>
</tbody>
</table>

*Chi-square test, p < 0.05, statistically significant
**Independent sample test, p < 0.05, statistically significant
ABG: air-bone gap; dB: decibel, Hz: hertz

**Table 4:** Analysis of postoperative AC and BC gain at individual frequencies

<table>
<thead>
<tr>
<th>Prep-Postop AC (Hz)</th>
<th>With vein graft Mean ± SD</th>
<th>Without vein graft Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC 250</td>
<td>27.08 ± 3.28</td>
<td>34.17 ± 2.93</td>
<td>0.119</td>
</tr>
<tr>
<td>AC 300</td>
<td>28.61 ± 3.21</td>
<td>41.50 ± 2.55</td>
<td>0.003*</td>
</tr>
<tr>
<td>AC 1000</td>
<td>26.53 ± 2.79</td>
<td>36.50 ± 2.49</td>
<td>0.011**</td>
</tr>
<tr>
<td>AC 2000</td>
<td>20.42 ± 3.29</td>
<td>26.72 ± 2.89</td>
<td>0.165</td>
</tr>
<tr>
<td>AC 4000</td>
<td>11.11 ± 3.92</td>
<td>20.0 ± 3.34</td>
<td>0.096</td>
</tr>
<tr>
<td>AC 6000</td>
<td>2.64 ± 4.24</td>
<td>11.83 ± 4.14</td>
<td>0.130</td>
</tr>
<tr>
<td>AC 8000</td>
<td>0.69 ± 3.82</td>
<td>5.83 ± 4.33</td>
<td>0.375</td>
</tr>
<tr>
<td>BC 500</td>
<td>1.94 ± 2.14</td>
<td>6.00 ± 1.80</td>
<td>0.161</td>
</tr>
<tr>
<td>BC 1000</td>
<td>4.17 ± 2.50</td>
<td>9.50 ± 2.09</td>
<td>0.115</td>
</tr>
<tr>
<td>BC 2000</td>
<td>3.06 ± 2.36</td>
<td>6.00 ± 2.04</td>
<td>0.359</td>
</tr>
<tr>
<td>BC 4000</td>
<td>-1.94 ± 2.62</td>
<td>7.33 ± 2.51</td>
<td>0.014*</td>
</tr>
</tbody>
</table>

AC: air conduction; BC: bone conduction
*Independent sample t-test, p < 0.05, statistically significant
Correlation analyses revealed positive correlations between preoperative vertigo and postoperative vertigo ($r = 0.371, p = 0.002$), between postoperative vertigo and postoperative loud noise intolerance ($r = 0.376, p = 0.034$), between preoperative tinnitus and postoperative tinnitus ($r = 0.271, p = 0.028$), and between postoperative tinnitus and postoperative vertigo ($r = 0.281, p = 0.022$; Spearman’s correlation).

**Revision surgery:** There were four cases that had revision surgery. All of them were in Group A. In two of them, it was noticed that the teflon piston was rather short and displaced; in one, prosthesis was fixed with fibrous tissue, and in the other one, the fenestration was closed with otosclerotic process.

**DISCUSSION**

Various sealing materials such as periosteum, fascia, fat, blood, connective tissue, perichondrium and vein have been used over the years in stapes surgery$^{[9,10]}$. In a recent study which compared fat, fascia and vein, satisfactory hearing outcomes were reported with no significant differences$^{[11]}$. Nevertheless, vein graft is mostly preferred to other living tissue grafts, because it is the only tissue containing sufficient elastic fibers to provide compliance and resistance.

Lopez et al reported a histologic study on vein grafts showing that vein graft becomes integrated into the middle ear mucosa, eventually overlaid by middle ear epithelium$^{[12]}$. However, fibrous reactions, reossification below the graft and graft lateralization have been reported in revision cases$^{[9,13]}$. Biomechanical studies show that interposition of a vein graft introduces an additional stiffness to the system, thus resulting in decreased hearing at speech frequencies$^{[14]}$. Marquet argued that if tissue graft was used as a seal, the long term result would only be the endothelial layer. Adjusting the length of the piston would be another hard task which would result in poor functional results$^{[3]}$.

On the other hand, Causse argued that sealing the stapedotomy hole with a large vein graft results in improved hearing both at high and low frequencies$^{[2]}$. Similarly, Portmann and Shea Jr. have reported up to 90% success rates with vein interposition$^{[15,16]}$. Marquet has also presented excellent functional results, especially characterized by a relatively greater percentage of closure of the ABG in higher frequencies, with his series of 5000 patients who underwent small fenestra technique without any interposition$^{[3]}$. In the latest analysis of his series, 81% success has been reported in 1681 otosclerosis operations. 85% of these surgeries were stapedotomies without interposition and the results of these stapedotomies were comparable with the partial and total stapedotomies with interposition. After a mean follow-up period of 5 years, stapedotomy scored even better for all frequencies$^{[17]}$.

Lately, Bittermann et al compared the results of primary stapes surgery with and without a vein graft in a retrospective multicenter international study$^{[7]}$. Despite some limitations discussed, the success rate with interposition was significantly higher than without interposition. They pointed out that differences in the surgeon, piston type, or technique used in opening the stapedotomy hole may have interfered with the postoperative results. Except for this study, our review of the literature failed to reveal any other study comparing stapedotomy with and without vein interposition.

Therefore, we also decided to evaluate the effect of vein graft interposition in our small group of case series. In this study, the patients were operated within the same clinic, but, although the study was retrospective, the piston types did not differ between the groups and the stapedotomy technique was the same except for vein graft interposition. One of the flaws was that for each technique, the majority of the stapedotomies were performed by one experienced surgeon, and comparing the outcomes became more a comparison of surgeons and their techniques, rather than simply the presence and absence of a vein graft. However, it is likely that every ear surgeon adopts a specific technique and uses it along his/her practice. In the similar study mentioned above, the methodology was the same, so that one technique was performed by one surgeon while the other was performed by two other surgeons. Even though the results of the study should be interpreted with caution, as the number of patients was small, it is improbable that the results would change in larger study groups. A power analysis of the comparison of mean postABG of the two groups reveals a power of almost 80% with the current number of patients in the study groups. Since the study was retrospective, the patients were not randomized. However, the analysis of preoperative characteristics did not reveal any differences between groups (Table 1).

The mean postABG of 66 cases was 13.8 dB, and the overall success rate was 47% in our series. In 77.3% of the cases, the postABG was ≤ 20 dB. Our success rates were somewhat lower than the literature, but most surgeons stress on the difficulty of reaching high success rates. Our review of recent studies which included higher frequencies for ABG calculation demonstrated that ABG closure to within 10 dB was achieved in 54% to 94% of patients (Table 5)$^{[5-7,18-25]}$.

The mean preoperative ABG was 35.3 dB. In our clinic, we tend to operate on patients with preoperative ABG over 30. However, in the series of most of the...
recent studies, the mean preoperative ABG is reported to be below 30 dB\cite{5,6}. It is reported that smaller preoperative ABG at frequencies under 1 kHz and preoperative AC thresholds below 50 dB are expected to yield statistically better results\cite{23,26}.

Despite our low success rates, the overall mean postoperative AC and BC thresholds of our series is comparable with literature. In Table 5, it is seen that our mean postoperative AC threshold (35.1 dB) was comparable to other studies, and in fact, our mean postoperative BC threshold (21.3 dB) was the second best value. The results of the cases without vein interposition are even better (29.3 dB and 18.6 dB for postoperative AC and BC thresholds, respectively). Our overclosure values were also high.

Evaluation of audiometric results can affect the level of success. Inclusion of 4 kHz instead of 3 kHz in the ABG calculation may have resulted in lower rates of success. Klievsky et al reported that when 4 kHz was included in the ABG calculation, the success rate of closure to less than 10 dB decreased by 7%\cite{10}. Our success rates were 52.8% for interposition group and 88% for the group without interposition when 3-frequency (500, 1000 and 2000 Hz) preoperative BC and postoperative AC thresholds were used to compute the postABG\cite{27}.

Higher success rates (66.7% vs. 30.6%) and lower post ABG results (10.7 dB vs. 16.4 dB) were achieved for the group without interposition. The success rates were significantly higher for the group without interposition at all frequencies. The mean postABG was higher at all frequencies in the interposition group, and significantly higher at frequencies 500 and 2000 Hz (Table 3). In our group of cases, performing vein graft interposition resulted in residual ABG.

In the original Causse technique, a 0.8 mm hole is created in the posterior third of the footplate and 0.4 mm stapes prosthesis is placed on a large vein graft so that a 0.2 mm wide elastic membrane is created between the prosthesis and the footplate\cite{2}. In our study, 0.6 mm pistons were mostly used in the vein interposition group. In this situation, the elasticity of the system may not have been enough to produce the required energy. A 0.4 mm piston could have resulted in better outcomes. Another reason for the failure in interposition group could be the technical difficulties in the preparation of the graft. The insufficient cupping of a rather thick graft might have resulted in failure in the contact of the prosthesis to the inner ear. This was observed in one of the revision cases.

High frequency SNHL was observed in 5 cases with vein graft interposition, and in no cases without interposition. Comparison of BC thresholds at 4000 Hz also revealed a higher rate of SNHL in the interposition group, but both of these parameters were insignificant. Comparison of the postoperative gain at 4000 Hz for BC, however, showed a significant higher gain for the group without interposition, and there was a SNHL of 1.94 dB in the interposition group instead of a gain. Similar loss in BC threshold at 4000 Hz has been reported in some series both with and without interposition. In the series of Klievsky et al without interposition, the mean BC threshold at 4000 Hz was raised from 23.9 to 25.3 dB, while in the series of Vincent et al, a 3.6 dB increment was seen in the postoperative BC threshold at 4000 Hz with Causse technique\cite{5,6}.

In the literature, both techniques result in similar complication rates. In the latest series of Marquet, the incidence of SNHL and perilymphatic fistula rate
was reported to be 0.91% and 0.26%, respectively[17], while Vincent et al reported postoperative SNHL > 15 dB and postoperative fistula rate as 0.5% and 0.3%, respectively[9]. However, the disadvantage of the large vein graft interposition technique is the difficulty in performing the technique and that it requires more skill than the small fenestra technique without interposition[9]. The vein grafts may not have been placed properly in some of the cases in the interposition group. With more manipulations and components to the surgery, surgery becomes more difficult and this may explain the differences demonstrated in the outcomes presented herein.

Postoperative vertigo is reported in 10 - 26% of the cases in the literature[20,28]. In our series, 31.8% of the cases had vertigo in long-term follow-up. However, we noticed that the same amount of patients reported vertigo preoperatively. Preoperative vertigo may be caused by an otosclerotic foci producing vestibular end-organ and/or neural degeneration, contacting vestibular labyrinth and changing biochemistry of the perilymph, or obstructing the vestibular aqueduct and creating a disturbance of the outflow and/or absorption of endolymph. Preoperative vertigo is considered to be a predisposing factor for postoperative vertigo and poor hearing results[29].

In the literature, 42 - 90% of patients with otosclerosis are reported to have preoperative tinnitus. 40 - 80% of the patients with tinnitus report an improvement postoperatively[28,30,31]. In our series, 66% of the cases with tinnitus recovered, while tinnitus developed postoperatively in two patients with vein graft. There were no differences in the frequency of postoperative vertigo, tinnitus, hyperacusia and taste disturbances between the two groups.

CONCLUSION

Doing a retrospective analysis is helpful in deciding which surgery yields favorable results. In this group of case series, vein graft interposition resulted in significantly higher hearing thresholds and tended to cause SNHL. The difficulties in the application of the vein graft may have caused the poor results in the interposition group. On the other hand, stapedotomy without interposition required less manipulation and led to satisfactory results without major complications. Prospective randomized studies with larger series comparing different techniques are required to better evaluate the results. Nevertheless, it is known that experience is the most important determinant of success in stapes surgery. Surgeons should keep track of the results of the surgeries they have performed, and choose the most convenient technique according to their comfort level and success.

REFERENCES


Acute Appendicitis Induced by Cholesterol Crystal-Embolism

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ABSTRACT

Cholesterol crystal embolism (CCE) or athero-embolism is a disorder caused by embolization of cholesterol-containing material, from the aorta and/or its great arteries, to various tissues in the body. We report a 74-year-old man who developed CCE as manifested by livedo reticularis, ischemic toes and protracted renal failure, one month after a femoral approach for coronary angioplasty. One month later, he developed acute abdomen due to acute appendicitis with peritonitis as confirmed by CT scan, laparoscopy and histopathology. It revealed an inflamed appendix, yet with a patent lumen. Its submucosal artery was occluded by multiple biconvex clefts indicating previous deposition of cholesterol crystals. The patient improved after appendicectomy, yet had required maintenance hemodialysis for his protracted renal failure.

KEY WORDS: atheroembolism, atherosclerosis, cholesterol crystals

INTRODUCTION

Disseminated cholesterol crystal embolism (CCE), or cholesterol atheroembolism, is a severe complication of atherosclerosis. It may occur spontaneously, but more often follows radiological/cardiological interventional procedures or vascular surgery in the aorta or its major vessels[1]. It usually presents as a systemic disease with multiple organ involvement including kidneys, skin, peripheral arteries and gut[2]. Gastrointestinal (GI) involvement may dominate the clinical presentation or present along the course of the disease mimicking a primary GI disorder[3]. Its GI manifestations include bleeding, diarrhea, hepatic failure, cholecystitis and pancreatitis[4]. However, appendicular disease was rarely reported.

CASE HISTORY

A 74-year-old man presented with progressive renal failure and painful lesions of both feet over the past one week. He had hypertension for more than 30 years and was a heavy smoker for most of his life. One month prior to his transfer to our unit, he suffered an acute myocardial infarction (MI) followed by unstable angina. Hence, he was subjected to coronary angiography through femoral route, which had revealed diffuse three vessel disease with left ventricular ejection fraction of 30%. Angioplasty and stenting of left circumflex artery was done at the same sitting. Three weeks later, he presented with easy fatigability, oliguria, bluish mottling of toes, with pain and tenderness in both feet. He was conscious, and oriented X3. He was afebrile and BP was 160/100 mmHg. He had weak dorsalis pedis pulses bilaterally. Systolic bruits were heard over both carotids, abdominal aorta and both femoral arteries. His feet were cold with tender purple-blue discoloration. Systemic examination did not reveal an abnormality. His laboratory parameters showed low hemoglobin at 92 g/L with normal mean corpuscular volume (MCV). Peripheral leukocyte and platelet counts were normal. Serum urea and creatinine were elevated at 28 mmol/L and 398 umol/L, respectively. Serum sugar,

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electrolytes and liver function tests were within normal limits. Urine showed 2(+) proteins with 8 - 18 RBCs/HPF, yet no pyuria. Serum protein electrophoresis and complement 3 and 4 were normal. Anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor, cryoglobulins, hepatitis B surface antigen and anti-hepatitis C antibodies were normal. Blood cultures were sterile. Serum troponin levels on admission were normal. He was managed, conservatively, as a case of post angiography CCE. He required continuous venovenous hemofiltration (CVVHF), which was carried out without systemic anticoagulation using saline flushes of tubes and filter. His initial hospitalization was stormy with multiple complications, including gangrenous changes in his toes, recurrent angina with elevated troponin levels, flash pulmonary oedema and abdominal pains with GI bleed. Interestingly, his colonoscopy was normal and upper GI endoscopy revealed mild gastritis, negative for H pylori. After one month of hospitalization in the renal unit, he developed acute, severe and progressive pain in right iliac fossa with local guarding and tenderness. Laboratory investigations at that time, showed neutrophilic leucocytosis with normal serum electrolytes and liver functions. CT scan revealed extensive atherosclerotic plaques in abdominal aorta with edematous appendix with lymphadenopathy and stranding of its mesenteric fat (Fig 1). The rest of viscera were normal. Since the picture was compatible with acute appendicitis, an emergency laparoscopy was carried out. The latter revealed an acutely inflamed appendix with small amount of serous fluid around appendix and in pelvis. Laparoscopic appendectomy was done, and operative culture failed to grow any organism. The gross examination of the resected area showed a 4 cm appendix with no fecolith in it. Histopathological examination revealed an acutely inflamed appendix with evidence of local peritonitis. Most arteries were showing atheromata with cholesterol clefts with segmental wall loss indicating chronic inflammation (Fig 2). Moreover, the appendicular wall showed loss of mucosa with pus cells associated with fibrinous exudate covering a densely fibrotic submucosa indicating chronic ischemia (Fig 3). The patient had an uneventful recovery without abdominal sequelae. Unfortunately, he remained dialysis-dependent. He had recurrent unstable angina with severe heart failure and recurrent aspiration pneumonia. Three months after his appendicectomy, he suffered massive MI with cardiogenic shock and could not be saved.
DISCUSSION

CCE represents an increasing cause of morbidity and mortality in the ageing population, with a prevalence rate as high as 15% in autopsy series of patients with atherosclerosis and aortic manipulations[1]. The cholesterol crystals dislodge and occlude small muscular arteries in the macrocirculation, resulting in tissue ischemia and necrosis[2]. Smaller particles may dislodge in arterioles and are not cleared by phagocytosis and may persist in the body for months. A foreign body type inflammatory response to the cholesterol material develops with eosinophilic and neutrophilic infiltrate, giant cell granuloma, intimal proliferation and subsequent fibrosis of the blood vessels with additional occlusion of the lumen[3].

Atheroemboli to the GI tract are not uncommon and represent an important and often unsuspected cause of abdominal manifestations[4]. Involvement of the digestive tract varies from 18 to 48% and may occur at any site along its length, producing many often misleading presentations[4]. The clinical spectrum of CCE in one study ranged from a catastrophic presentation with bowel infarction or pancreatitis to a more indolent vasculitic form such as chronic diarrhea and eosinophilia[4].

The most common modes of GI presentation of CCE are hemorrhage and abdominal pain[3,4,5]. GI bleeding is due to mucosal ulceration and mucosal infarcts. On the other hand, abdominal pains are associated with non-infarct ischemia or less frequently, intestinal infarction and perforation involving both the large and small bowel. Pancreatitis is reported rarely, despite frequent embolization to the organ[6]. Other rare but reported cases include overt hepatitis[8], chronic acalculous or acute necrotizing ischemic cholecystitis[7,8], pseudopolyp formation and bowel obstruction secondary to stricture formation[9,10].

Acute appendicitis is rare in the elderly and the clinical features can be variable. Obstruction to the narrow appendiceal lumen usually initiates the clinical illness of acute appendicitis. Obstruction has multiple causes, including lymphoid hyperplasia, fecaliths, parasites, foreign bodies, Crohn’s disease, primary or metastatic cancer and carcinoid syndrome[11]. In some cases, no evident cause is discernable. In our patient, the lumen of the appendix was patent. Moreover, histopathological examination of the appendix revealed occlusion of the appendicular artery by multiple cholesterol clefts associated with dense submucosal fibrosis associated with culture-negative acute appendicitis. These features indicate a major role of frequent CCE in the development of appendicitis in this patient. Literature review indicates that appendicular CCE was reported in an isolated case of an autopsy series by Moolenaar[3]. Hence, to the best of our knowledge, our case is the first reported clinical presentation of acute appendicitis secondary to CCE.

CONCLUSION

Acute appendicitis should be included in the differential diagnosis of acute abdomen in patients with CCE.

REFERENCES

Case Report

A Rare Large Low Rectal Melanoma

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ABSTRACT—
Rectal melanoma is a very rare and fatal disease. In this report, we present the case of a 49-year-old lady who was presented with bleeding per rectum. Examination and investigations revealed a low rectal melanoma with metastasis. A wide local excision of the bleeding mass was done.

KEYWORDS: melanoma, rectal cancer, wide local excision

INTRODUCTION
Melanomas are malignancies which can affect any anatomic region where melanocytes exist (e.g., the epidermis, eyes, nasal cavity, oropharynx, vagina, urinary tract, rectum and anus[1]). The most common form of melanoma involves the epidermis and constitutes 91.2% of melanoma cases, followed by the eyes and nasal cavity[1]. Primary rectal or anorectal melanoma is a very rare and highly malignant disease[2]. Moore was the first person to report melanoma of the anus and rectum in 1857[3]. It is considered the third most common malignancy of the anorectal area[2]. Lesions are commonly found at the anorectum, followed by the anal canal and anal verge[1,2]. Also, the anorectum is the most common site for development of melanoma in the alimentary tract[1,2]. Rectal melanoma accounts for 0.2 - 0.3% of all melanoma cases[4]. It accounts for less than 1% of the primary anorectal malignancies[3]. The lesion is most often discovered in the fifth and sixth decade of life[6] with almost equal male to female ratio[6], but some studies have shown a female preponderance[4]. Anorectal melanoma is staged on a clinical basis, focusing on loco-regional and distant spread. Stage 1 is local disease only, stage 2 is a local disease with increased thickness and ulceration, stage 3 is local disease with involvement of the regional lymph nodes, and stage 4 shows distant metastatic disease[7]. The standardized evidence based treatment approach is not well defined due to the rarity of this disease[8]. Early surgery is the most effective treatment, either in the form of wide local excision (WLE) or abdominoperineal resection (APR) with comparable survival, since current chemotherapy and radiotherapy alone have been proven ineffective[9].

CASE REPORT
A 49-year-old female patient came to our surgical clinic in February 2015 complaining of 2 months history of bleeding per rectum with gradual increasing constipation over the last month and weight loss. The patient was diagnosed with hemorrhoids at a general clinic in which she received medications with no improvement. General and abdominal examinations were unremarkable except for moderate pallor and mild muscle wasting. Digital rectal examination including proctoscopy showed a well defined, globular, firm mass, around 4 x 4 cm and about 4 cm above the anal verge. The mass was bleeding on touch and no palpable inguinal lymph nodes were detected. The patient was admitted to the hospital and basic laboratory tests demonstrated severe anemia with hemoglobin of 77 g/L (RR: 120 - 150g/L) and hematocrit of 0.270 l/L (RR: 0.36 - 0.46 l/L). Colonoscopy was normal, except for the low rectal mass. A biopsy sample was obtained and histological examination was consistent with a melanoma. A computed tomography (CT) scan of the chest, abdomen and pelvis showed the mass with the presence of hepatic...
deposits (Fig 1). Magnetic resonance imaging (MRI) of the pelvis showed limitation of the mass to the bowel wall (Fig 2). Positron emission tomography (PET) scan demonstrated intense uptake at the site of the mass with the liver lesions. Further laboratory tests showed negative results for carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9) and human immunodeficiency virus (HIV). The level of lactic dehydrogenase was 126 IU/L (RR: 90 - 180 IU/L). The condition was explained to the patient and the need for excision of the bleeding mass as a palliative treatment along with postoperative adjuvant therapy. After correction of anemia, a trans-anal WLE was done with musculo-cutaneous flap and primary closure (Fig 3, 4). The resected specimen measuring about 5 x 4 cm was a firm, pedunculated mass with ulceration (Fig 5). The histopathological examination showed anaplastic melanocyte and the immunohistochemical examination showed positive for Melan-A, HMB-45 and S-100 with a final diagnosis of melanoma. The patient tolerated the procedure well with uneventful postoperative recovery and she was referred to the oncologist where chemotherapy was started. At the 6-month follow up, the patient was doing well with no evidence of local recurrence.

Fig 1: A CT scan of the abdomen showing the presence of hepatic deposits

Fig 2: MRI of the pelvis showing limitation of the mass to the bowel wall

Fig 3, 4: Trans-anal WLE was done with musculo-cutaneous flap and primary closure
DISCUSSION

Primary rectal or anorectal melanoma is an uncommon, highly malignant tumour associated with an extremely poor prognosis despite aggressive surgical treatment[9]. It is generally present with rectal bleeding and a sensation of a mass, which is usually diagnosed as hemorrhoid[10]. Other common symptoms[11] are tenesmus and bowel habit changes. Due to these benign symptoms, early diagnosis is difficult[10]. The average time from the onset of symptoms to diagnosis is about four months[5]. This delay obviously contributes to the poor prognosis, as up to one-third of the patients already suffer from dissemination at the time of diagnosis[5]. Risk factors remain unknown, but unlike cutaneous melanoma, rectal melanomas are not influenced by sunlight exposure[12]. Some researchers have implicated an association between anorectal melanoma and HIV or the tumorigenic Human Herpes Virus-8, but this relationship is also unclear[12]. The Clark level and Breslow index used for evaluation of cutaneous melanoma are not applicable to extra-cutaneous melanoma[13]. It has been shown that an important determinant of prognosis for any primary melanoma is the tumor thickness. Specially, thin lesions (< 1 mm) have a more furable prognosis than thick (> 4 mm) lesions. However, there are cases of long-term survival in spite of the presence of thick lesions or lesions of intermediate thickness (1 – 4 mm)[12]. Others reported that longer survival rate was shown in tumors less than 5 cm in diameter and a depth of invasion confined to the muscularis propria[14]. It was also mentioned that the predicted factors for poor prognosis are the advanced nature of the disease at the time of diagnosis, ulceration, the rich vascularity of the rectal mucosa and the high biological aggressiveness of the tumour[15]. Due to its low incidence, experience in treatment is limited and the optimum surgical intervention is controversial, ranging from radical APR to WLE alone[16]. Controversy remains regarding the better option. The APR gives better control of the local disease but without clear improvement in the survival, while sphincter preserving WLE avoids the need for stoma but can be complicated with incontinence[14]. Some retrospective studies have revealed a statistically significant improvement in loco-regional control with APR compared with WLE alone, but if the WLE is combined with loco-regional radiotherapy, it results in the same control and less loss of function[16]. Other studies have recommended only a sphincter saving excision for two reasons. Firstly, treatment is often palliative and wide radical surgery is unnecessarily mutilating. Secondly, tumour stadium and biological behavior of the tumour determines survival instead of the choice of the surgical operation[5]. Overall, many authors in the literature have found no difference in overall survival and the disease free interval between patients who had curative APR and those who were treated with WLE[5,10,15,17]. Slingluff and Cooper reported that the five year survival rate was less than 10%[17]. Weinstock also reported the same rate even if radical surgery such as APR and chemotherapy are performed[18]. Other reviews in the literature such as Iddings et al reported on patterns of treatment and outcome in patients with anorectal melanoma from the SEER database and found no significant difference in 5-year survival between patients undergoing APR versus WLE (17% and 19%, respectively)[19]. Nilsson et al found that margins of resection significantly predicted long-term advantage, with 5-year survivals of 19% for patients receiving an R0 resection, compared to 6% for patients with R+ resections, regardless of the type of surgery[20]. However, Myoclinic reported the five year survival rate as 22% and cure in 16% in their study[18]. Systemic chemotherapy is indicated for the disseminated and lymph node positive disease, but the effect of these agents on overall survival remains unknown[19]. The other modality of adjuvant therapy, i.e. radiation, is well tolerated and is promising in improving loco-regional control. Post-operative radiotherapy may improve loco-regional control after WLE. Definitive assessment of the efficacy of adjuvant radiation therapy requires further prospective studies[21]. The combination of interferon, interleukin-2 and cytotoxic drugs, termed biochemotherapy or chemoimmunotherapy, seems to be more active than any agent alone in the treatment of metastatic disease[22]. Rectal melanomas spread to
the mesentric and iliac lymph nodes, but most of the studies were done on the anorectal melanoma which spreads through inguinal as well as mesentric lymph nodes, and therefore they suggested the combination of APR with bilateral inguinal lymph node dissection[23]. Other studies described a higher incidence of mesentric lymph node metastasis compared with groin lymph node metastasis. For this reason, they recommended APR alone as the best potentially curative surgery[23]. Lymph node dissection is indicated only in the presence of inguinal nodes but prophlactic dissection is of no value[24]. Sentinel lymph node biopsy is the preferred method for nodal staging in cutaneous melanoma, it’s role for staging anal melanoma remains unclear[23]. In our case, the patient presented with bleeding low rectal melanoma with metastasis which is considered incurable. Although the surgery is not the cure, it has a role in saving the patient from blood loss. Our choice was the WLE in addition to adjuvant therapy to avoid morbidity of the APR.

CONCLUSION
Rectal melanoma is a rare and fatal disease. Early diagnosis and multidisciplinary team management can have an important effect on the prognosis. Wide local excision is the treatment of choice with adequate margins for controlling the local symptoms. The role of adjuvant radiotherapy, chemotherapy and immunotherapy looks promising, but further investigations are needed.

REFERENCES
Case Report

Pyeloduodenal Fistula: A Case Report

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ABSTRACT

Pyeloduodenal fistula is an extremely rare clinical entity. This case report describes a 40-year-old female who was admitted to our hospital with a history of on and off pain in the right hypochondrium and vomiting. Computed tomography (CT) confirmed an atrophic renal mass with staghorn stone that had eroded into the duodenum and caused an internal fistula. She had undergone right nephrectomy and closure of duodenal fistula. Her surgery was complicated by a small duodenal leak, which was successfully treated conservatively by percutaneous ultrasound guided drainage. We report briefly on the clinical features of this rare entity and also review and summarize the etiology, diagnosis and treatment options from the existing literature.

KEYWORDS: calculus, pyelonephritis, pyeloduodenal fistula, surgical treatment

INTRODUCTION

Spontaneous pyeloduodenal fistulas are extremely rare. There are almost 100 cases of pyeloduodenal fistulas reported since the first case description by Campaigniac in 1893[1,2]. These are divided into traumatic and spontaneous forms. In spontaneous fistulas, the primary disease process is, in most cases, of urologic origin: infected kidney stones, pyonephrosis, xanthogranulomatous pyelonephritis, renal tumors, and infected renal cysts[3-5]. In early literature, tuberculosis was a frequently associated cause of renal inflammation and associated with fistula formation. However, since the availability of effective anti-tuberculous treatment, few cases of pyeloduodenal fistula secondary to tuberculosis have been reported. Nephrectomy and primary closure of the duodenum are traditional treatment methods of non-traumatic pyeloduodenal fistula[6-8]. However, there are anecdotal reports of successful conservative management[6,8].

The present case of spontaneous pyeloduodenal fistula is secondary to advanced chronic pyelonephritis, staghorn calculus and focal xanthogranulomatous pyelonephritis. To the best of our knowledge, this is the first case report of a pyeloduodenal fistula from the United Arab Emirates.

CASE REPORT

A 40-year-old female was admitted in July 2015, with history of recurrent upper abdominal pain and vomiting. She gave a history of urinary tract infection in the past, treated symptomatically in her native country without ever having a complete workup, including abdominal imaging. She had a tubal ligation 15 years back. She also denied any history of tuberculosis in the past. Examination revealed an asthenic female with mild pallor and normal vitals parameter. Abdominal examination revealed a tender right hypochondrium without any palpable mass. Her other systems were clinically normal. Her hematological, urinary, and biochemical parameters were essentially normal except for hemoglobin of 11.8 g/dL. An ultrasound examination of the abdomen showed a normal left kidney, and a giant stone in the right kidney with nearly absent renal parenchymal tissue.

Oral and intravenous contrast computed tomography (CT) abdomen showed large retroperitoneal right renal mass without cortex or medullary differentiation, which crossed and attached to Inferior Vena Cava (IVC), diaphragm and posterior abdominal wall (Fig 1). Urinary culture showed no growth. Initial treatment comprised of intravenous fluid and analgesic. Urological consultation was

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requested and a decision was taken for right nephrectomy and closure of the duodenal fistula.

On exploratory laparotomy, this renal mass was adherent to all retroperitoneal structures including IVC and diaphragm, making dissection extremely difficult. This mass was removed in two pieces without any inadvertent injury to surrounding structures and the duodenal defect was closed in two layers with serosal patch. A tube drain was kept in the kidney bed which was removed on the 4th post-operative day. Histopathology confirmed the diagnosis of pyeloduodenal fistula with total atrophy of renal parenchyma, and advanced chronic pyelonephritis with areas of focal xanthogranulomatous changes. Fibro-inflammatory process extended in the perinephric fat and to the irregular defect (fistula) site with associated hemorrhage and granulation.

Seven days later, she developed pain in the right hypochondrium, and a contrast CT abdomen revealed a well-defined collection with a small duodenal leak. Ultrasound-guided 14 F pigtail catheter was placed into the collection along with antibiotics and analgesics. She was allowed a regular diet as part of conservative management for her duodenal fistula. The catheter was removed three weeks later. During her recent follow up four months after surgery, she is doing extremely well and is without any symptoms.

DISCUSSION

Pyeloduodenal fistula is a rare but serious condition generally associated with chronic inflammatory renal disease, trauma or malignancy. All divisions of the alimentary tract with the exception of the esophagus, have been implicated in various types of nephrointestinal fistulae[9]. Pyelocolic fistulas account for about 60% of the uroenteric fistulas of the upper urinary tract, followed by pyeloduodenal forms, renogastric, and finally renojejunal[13]. It is believed that inflammation, urinary extravasation, abscess formation, and perinephric inflammation are the main pathophysiologic mechanisms of non-traumatically caused pyeloduodenal fistula[10]. The posterior aspect of the second portion of the duodenum lies in close proximity to the medial portion of the kidney and renal pelvis. When perirenal inflammation takes place, the portion of the duodenum is more easily involved because of the relative immobility of the second part of the duodenum and its lack of a posterior peritoneal covering[6,11]. Our case developed fistula as described above. Traumatic pyeloduodenal fistula can occur from trauma, surgery and interventional procedures[6].

Symptoms that have been reported include a variety of urinary tract, gastrointestinal, and constitutional symptoms as a result of the involvement of both the digestive and urinary systems. In many reviews, it has been pointed out that as insidious and progressive asymptomatic pyelonephritis was an attendant clinical condition, gastrointestinal symptoms should be considered as an important clue for diagnosis[1]. Frequently, the symptoms can be correctly interpreted only after the diagnosis is established. The pathogenic symptoms rarely occur in the setting of upper urinary tract fistulas (fecaluria, pneumaturia), and often the diseased kidney becomes non-functional[3], like in our present case report where clinical history was silent. In case of fistulas of traumatic origin, the symptoms of both gastrointestinal and peritoneal origin dominate the clinical picture[3,10-11].

Diagnosis of the pyeloduodenal fistula requires the urinary symptoms. Retrograde pyelography is the method of choice which demonstrates the fistula in 64% of the cases[7]. Other reported studies include antegrade pyelography and upper GI series[6]. Nowadays, contrast CT abdomen is the best modality of imaging for demonstrating the nature, location, and extent of the underlying renal fistula[3,8].

Nephrectomy and primary closure of the duodenum are traditional treatment methods for non-traumatic spontaneous pyeloduodenal fistula[6-8]. Either a transperitoneal approach or retroperitoneal approach may be used. The retroperitoneal approach in the face of active suppurition will avoid contamination of the abdominal cavity[6-7]. In contrast to such cases, every effort should be made in patients with traumatic pyeloduodenal fistula to salvage the functioning kidney. Recent advances in technology for percutaneous renal surgery have led to reports of several successful experiences with conservative treatment, providing encouragement that new and successful treatments can be developed[11]. Due to the poor prognosis of newer surgical management,
it is suggested that any attempt to spare the kidney should be avoided when the primary disease process is apparent in the kidney for a long time\(^6\). In our case, though we did nephrectomy and primary closure of the fistula, it was complicated by the duodenal leak which was successfully managed by percutaneous drainage.

CONCLUSION
Pyeloduodenal fistula is an extremely rare clinical entity. Due to the poor prognosis of newer innovative surgical management, nephrectomy and primary closure of duodenal fistula should be the aim for the management of non-traumatic spontaneous pyeloduodenal fistula.

ACKNOWLEDGMENT
The authors thank and are highly indebted to Mr. Mohammed Mudassir Anwar Ali for his secretarial assistance in preparation of this article.

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Case Report

Pregnancy in Fahr’s Disease: A Rare Case Report

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ABSTRACT

Fahr’s disease (FD) is a rare, neurological disorder characterized by abnormal calcified deposits in basal ganglia. The clinical characteristics are various and usually appear due to dysfunction of the affected areas. According to our knowledge, FD in pregnancy has not been reported previously. In this paper, we report a 28-year-old pregnant woman who was diagnosed to have FD 3 years ago. The patient was followed-up during pregnancy and she had no symptoms related to FD. Her pregnancy was uneventful until the day of delivery. The objective of this case report is to describe the clinical course for this rare condition in pregnancy.

KEY WORDS: bilateral calcification, fahr’s disease, prognosis, pregnancy

INTRODUCTION

Fahr’s disease (FD) is a rare neurodegenerative disorder of unknown cause characterized by sporadic or familial idiopathic basal ganglia calcification that is associated with neuropsychiatric and cognitive impairment[1]. It was first described by Karl Theodor Fahr in 1930. The prevalence of FD is not known, but is more common in men. The diagnosis of FD is made by exclusion of other conditions that may also cause bilateral calcification of the brain regions[2]. There was no case report or article on Pubmed about FD and pregnancy. Pregnancy could have been affected negatively by several symptoms of FD, such as tetany, spasticity, gait disorder, speech impairment, chorea, tremors, dystonia, myoclonus, clumsiness, fatigability, unsteady gait, slow or slurred speech, dysarthria dysphagia, involuntary movements and muscle cramping[3]. However, our case had no symptoms related to FD. Herein, we report this case report to emphasize the clinical features and good prognosis of FD during pregnancy.

CASE REPORT

A 28-year-old woman presented with headache, dizziness, dysarthria and numbness in her hands 3 years ago. She was diagnosed with FD by physical, laboratory and radiological examinations. Cranial computed tomography (CT) showed bilateral symmetric calcifications in the caudate and lentiform nuclei, thalamus and cerebral gyrus (Fig 1). The patient was followed-up in our hospital over the last two years and conceived spontaneously in February 2015. This was her first pregnancy. She had no history of movement or cognitive disorder. There were no neurological or genetic disorders in the family. She had no symptoms related to FD during the course of the pregnancy. Her vital signs were stable and her blood pressure was normal. Systemic and neurological physical examinations were also normal.

Laboratory examinations were within normal limits for complete blood counts, renal and liver function tests, serum calcium, phosphorus, magnesium, alkaline phosphatase, parathyroid hormone, 25-OH-vitamin D and thyroid hormones during pregnancy (Table 1). She didn’t have any health problems related with pregnancy or another cause. Her pregnancy was uneventful until delivery. A female neonate was delivered by caesarean section at 38 weeks because of cephalopelvic disproportion. She delivered a healthy baby with a birth weight of 3.8 kg with a good Apgar score. Her intraoperative
and postoperative course was uneventful. She was discharged in satisfactory condition on the second postpartum day.

DISCUSSION

Fahr’s disease may be either sporadic or familial. The familial types of FD are most commonly reported as being due to autosomal dominant or rarely autosomal recessive inheritance. A locus at 14q has been suggested to be commonly involved in the genetic transmission of FD[4]. This presented case was accepted as sporadic due to lack of FD in her family. The prevalence of FD is unknown, but an incidence of intracranial calcifications ranging from 0.3% to 1.2% had been reported in routine radiological examinations[3]. The presented case had intracranial calcifications.

The etiology and pathophysiology of the FD are still unknown. Neuropathological studies have shown intracerebral bilateral mineral deposits composed of nonatherosclerotic calcium in the walls of small vessels. In FD, basal ganglia calcifications may be seen secondary to infectious, inflammatory, metabolic and genetic diseases. The most common metabolic disorders similar to FD are parathyroid and calcium abnormalities[6]. Our patient did not have any abnormality in calcium, phosphate and parathyroid hormone levels.

Patients may remain symptom-free but approximately two-thirds of the patients are symptomatic. Typical presentation starts between 4th and 5th decade of life. This patient’s illness had been diagnosed in the third decade. FD is generally characterized by extrapyramidal symptoms such as Parkinson’s tremor, dystonia or cerebellar ataxia. Other neurological and psychiatric symptoms may include events such as stroke, seizures, syncope, psychosis or dementia[7]. Our patient did not have any extrapyramidal or psychiatric symptoms. Similar cases have been reported in the literature[8].

The diagnosis of FD is made using a combination of clinical features, brain imaging, and exclusion of other causes of intracranial calcification. CT is a common method for the diagnosis of FD. The most common area of calcification is globus pallidus, but other intracerebral areas such as putamen, caudate nucleus, dentate nucleus, thalamus, cerebral cortex and cerebellar hemispheres may be involved[9]. The CT scan revealed calcifications in bilateral basal ganglia, capsula interna, thalami, and the bilateral cerebellar hemispheres in our case.

Fahr’s disease is usually treated for the related symptoms. There is no specific treatment for etiology and progression of FD[10]. Serum calcium level needs frequent monitoring in pregnant patients with

<table>
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<th>Table 1: Laboratory findings of the patient</th>
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<td>Serum parameter</td>
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SGPT: serum glutamic-pyruvic transaminase; SGOT: serum glutamic oxaloacetic transaminase; TSH: thyroid-stimulating hormone; fT4: free T4; 25 OH D3: 25-hydroxy vitamin D

Fig 1: Cranial computed tomography images showing calcification in the brains of patients with Fahr’s disease

and postoperative course was uneventful. She was discharged in satisfactory condition on the second postpartum day.
FD. It should not be allowed to fall below 8 mg/dL to avoid preterm labor or midtrimester abortion. Hyperventilation during labor may precipitate hypocalcemia and tetany\textsuperscript{[11]}. In our case, calcium metabolism was normal during pregnancy.

**CONCLUSION**

Fahr’s disease is a chronic, slowly progressive and neurodegenerative disorder. Here we presented a rare case report with FD and pregnancy. The patient did not have any adverse event related to FD during pregnancy. Finally, at least in our patient, FD did not have any negative effect on the pregnancy.

**ACKNOWLEDGMENT**

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**Conflict of interest:** There are no potential sources of conflict declared by any of the authors.

**Ethical approval:** Written informed consent was obtained from the patient for publication of this case report.

**REFERENCES**

Case Report

Papillary Carcinoma of Lingual Thyroid with Cervical Nodal Metastases and Absence of an Orthotopic Thyroid Gland: A Case Report and Review of Literature

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ABSTRACT

Lingual thyroid is a rare developmental abnormality characterized by the failure of the thyroid gland, or remnants, to descend from anywhere along its embryologic path of origin at the foramen caecum to its normal eutopic pretracheal position. The reported prevalence of lingual thyroid is 1 in 100,000, and it is more common in females, with a female to male ratio ranging from 3:1 to 7:1. Carcinoma of the lingual thyroid is even more unusual with less than 1% of lingual thyroids undergoing malignant transformation. Only 40 cases have been reported in the world literature. Herein, we present an uncommon case of papillary carcinoma of lingual thyroid with bilateral cervical nodal metastases in an elderly female with the absence of an orthotopic thyroid gland. Ours is an unusual case report analyzing the diagnostic and therapeutic issues, surgical management strategies and treatment outcomes related to this rare disease entity.

KEY WORDS: dysphagia, ectopic thyroid, hypothyroidism, papillary thyroid carcinoma

INTRODUCTION

Lingual thyroid is a rare congenital anomaly, originating from aberrant embryogenesis, and characterised by the failure of the thyroid gland, or remnants, to descend from the foramen caecum to its usual pre-laryngeal site. Lingual thyroid is relatively uncommon, and carcinoma of the lingual thyroid is extremely rare, with less than 40 cases reported. Lingual thyroid (at tongue base) is the most frequent ectopic location of the thyroid gland, although the reported prevalence of lingual thyroid is 1 in 100,000 to 300,000 in the general population\textsuperscript{1,2} with a female predominance. Ectopic thyroid tissue can also occur above the hyoid bone (pre-laryngeal thyroid), between the geno-hyoid and mylohyoid muscles (sublingual thyroid), and in other rare sites such as the pharynx, trachea, oesophagus, lung, breast, mediastinum, precardial sac, heart, adrenal gland, duodenum and mesentery of the small intestine\textsuperscript{3-7}. The true prevalence of carcinoma arising in the lingual thyroid is probably underestimated, however, some authors report it to be 1%.

CASE REPORT

A 43-year-old female presented with swelling on both sides of the neck and a mass at the tongue base which had been present for many years with the sensation of a foreign body. The patient also referred to having dysphagia, dyspnoea and hoarseness of voice for 3 months. She was normotensive and non-diabetic. Lab investigations revealed normal haemoglobin concentration level of 13.2 g/dl (normal range: 13.5 - 17.5 g/dl) and serum calcium level of 9.8 mg/dl (normal range: 8.9 - 10.1 mg/dl). Hypothyroidism was diagnosed on the basis of biochemical findings: an elevated serum thyrotropin (TSH) level of 98.2 uIU/ml (normal range: 0.7 to 6.4 uIU/ml) and a low triiodothyronine (Free T3) level of 20 ng/dl (normal range: 80 - 180 ng/dl) and thyroxine (T4) level of 2.4 μg per deciliter (normal range: 6.0 to 14.2 μg/dl). Upon oropharyngeal examination, the patient presented an enlarging, hyperaemic pink, spherical mass measuring 4 cm in diameter. The mass was covered with intact mucosa, located at the base of the tongue, occupying the oropharynx and obstructing the visualisation of the
larynx. On palpation, the mass was firm, sessile, non-tender and did not bleed on touch. X-ray of the neck revealed large soft tissue opacity in both sides of the neck associated with anterior displacement of trachea (Fig 1). Cervical ultrasonographic (US) assessment showed multiple large well defined hypoechoic masses in the region of the neck bilaterally, lateral to carotid vessels, likely to represent nodal metastases. There was another midline heteroechoic soft tissue mass at the base of the tongue representing primary mass. Computed tomographic (CT) examination of the neck revealed aberrant thyroid tissue as a low density solid mass, measuring 32.4 x 22.5 mm, with distinct margins restricted to the base of the tongue, absence of an orthotopic thyroid gland and bilateral cervical nodal metastases (Fig 2). Contrast enhanced CT analysis of neck suggested heterogenous contrast enhancement of the mass (Fig 3). A thyroid scan with technetium Tc-99m sodium was performed showing a marked midline focal area of isotope uptake in the region of tongue base, thus representing a lingual thyroid. There was no thyroid uptake in the neck.

Review of these imaging findings of the neck revealed that the patient’s only thyroid tissue was located at the tongue base and was the site of the primary tumor with bilateral cervical nodal metastases. Following biopsy pathology, papillary lingual thyroid carcinoma was diagnosed. She was put on L-thyroxine (75 μg/day) for 15 days before surgery. Treatment with levothyroxine resulted in FT3, FT4 and TSH levels returning to normal ranges. Bilateral selective neck dissection with surgical excision of all the thyroid tissue by transoral total thyroidectomy was performed. The patient underwent a whole body radio-iodine scan (I\(^{131}\)) to detect any persistent disease. Post-operative thyroid scan suggested no evidence of any functioning thyroid tissue in the neck. Histopathological examination of the excised tissue further confirmed papillary carcinoma arising from lingual thyroid with intact capsule in the tongue base mass. Pleomorphic malignant oval to rounded epithelial cells with ground glass nuclei and nuclear grooves were seen. Immunohistochemical analysis
revealed positive thyroglobulin (TG), cytokeratin (CK), and thyroid transcription factor-1 (TTF-1) as diagnostic papillary thyroid carcinoma (PTC) markers. The surgical clearance and whole body radioiodine scanning was followed by radioactive iodine ablation and substitutive thyroid hormonal therapy. Since, post-operative magnetic resonance (MR) imaging showed no evidence of metastases, regular follow-up was advised every 3 months with clinical evaluation, thyroglobulin assays, and nuclear scintigraphy.

**DISCUSSION**

Ectopic thyroid gland is a rare embryological aberration, resulting from incomplete descent of the thyroid gland from the foramen caecum to its normal pretracheal location\[^1\]. Lingual thyroid is defined as the presence of thyroid tissue in the midline at the base of the tongue anywhere between the circumvallate papillae and the epiglottis. Previous studies reported hypothyroidism in 33 - 62% of all patients with ectopic thyroid\[^3,8\]. Carcinoma of the lingual thyroid is rarer, with an incidence of 1%, and less than 40 cases have been reported in the world literature\[^9-12\]. The imaging features of PTC in lingual thyroid are documented by only 11 studies\[^9-14\]. In all previous reported studies, masses were located within the tongue base, not protruding, with a well-defined round shape. However, in our case, the mass was located at the midportion of the tongue base and mainly protruding to the oropharyngeal cavity without extension towards the vallecula and lateral pharyngeal mucosal wall. We considered the mass at the tongue base to be lingual thyroid carcinoma because the mass is in the midportion of tongue base, is strongly enhanced after infusion of contrast with low attenuation on pre-contrast CT, and MRI showed high signal intensity on T2-weighted images and homogenously iso-signal intensity on T1-weighted images. Origin of the protruding mass from the lingual tonsil was ruled out because it showed low attenuation on pre-contrast CT. However, differential diagnosis of squamous cell carcinoma of the tongue base confused us. The enhanced MR images demonstrated strong enhancement - more pronounced than squamous cell carcinoma. This strong enhancement of the mass is similar to that of reported cases of lingual thyroid PTC. CT and MRI findings further verified the impression of the absence of an orthotopic thyroid gland and ectopic lingual thyroid to be the site of the primary tumor. The present report not only describes use of various imaging modalities but also highlights the predominance of papillary type in lingual thyroid associated carcinoma. This fact is probably related to the history of hypothyroidism and compensatory hyperplasia, secondary to the absence of an orthotopic gland. In terms of the surgical approach to lingual thyroid carcinoma, an oral, lateral cervical or even a transhyoid incision may be the best. The American Thyroid Association (ATA) also recommends total thyroidectomy for large tumors > 4 cm\[^15,16\]. As per ATA guidelines\[^17\], surgical excision of the lingual tumor should be followed by whole body radioiodine scanning in order to detect any persistent disease. Iodine-131 ablation should be done only when the pathologic characteristics so demand. The patient should be administered adequate doses of levothyroxine and regular follow up for intrathyroidal cancer by scanning and serial assays of thyroglobulin.

**CONCLUSION**

Findings in this case emphasize the rarity of the lesion and the significance of detailed clinical, radiological and histological analysis of a mass
located in the mid-portion of the tongue base region. Routine pre-operative work-up including history, thyroid function test and thyroid scan is a must in the evaluation of all cases of tongue base mass lesion.

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Sequential Bilateral Rectus Sheath Hematoma after Anticoagulation

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ABSTRACT
Bilateral rectus sheath hematoma (RSH) is extremely rare. Its causes are similar to those of unilateral RSH. However, its clinical manifestation is more serious, usually requiring surgical or endovascular intervention. We report a case of sequential bilateral RSH that was treated successfully. Reinitiating anticoagulation after RSH should be done cautiously, with consideration for the risks and benefits.

KEYWORDS: acute pulmonary thromboembolism, anticoagulation, coil embolization, hematoma

INTRODUCTION
Anticoagulation therapies such as warfarin and low-molecular-weight heparin have numerous indications such as atrial fibrillation, deep vein thrombosis, pulmonary thromboembolism, cardiac valve replacement, and acute myocardial infarction[1]. However, these medications can cause bleeding complications, including rectus sheath hematoma (RSH)[2]. We report a case of sequential bilateral RSH after anticoagulation.

CASE REPORT
An 84-year-old woman with a 10-year history of hypertension and mild dementia was admitted with acute pulmonary thromboembolism (PTE). Warfarin was initiated with concurrent unfractionated heparin. The patient developed sudden abdominal pain on the 9th day of admission, with a fall in blood pressure to 90/50 mmHg. Her hemoglobin level dropped from 11.6 to 7.3 g/dL. Computed tomography (CT) imaging (Fig 1) showed a left RSH with active bleeding (dotted arrow). Urgent coil embolization of the left inferior epigastric artery was performed. Her vital signs and hemoglobin level stabilized after embolization. We initiated low-molecular-weight heparin (LMWH) instead of warfarin in consideration of the acute PTE. However, the patient developed recurrent abdominal pain and her hemoglobin level decreased two days following the change to LMWH. CT imaging was repeated (Fig 2), which showed a left RSH with an embolized coil (dotted arrow) and a newly developed right RSH (white arrow). Coil embolization was then also performed for the right inferior epigastric artery. Her vital signs and hemoglobin level stabilized following embolization. The patient was closely observed for an additional 20 days, during which she did not show any further episodes of bleeding. She was subsequently discharged without complications. Clinical follow-up for 6 months did not show any bleeding episodes.

DISCUSSION
RSH is a rare but potentially life-threatening condition[2]. Damage to the epigastric arteries and their branches or direct damage to the abdominal muscle is the most common direct cause of anticoagulant-associated hematomas[2]. Other risk factors include advanced age, systemic anticoagulation, intraabdominal injections, abdominal wall strain, minor trauma, and pregnancy. Antiplatelet agents, including both LMWH and unfractionated heparin, can cause RSH[2]. Women are more prone to hematoma formation because they have less muscle mass and more flaccid abdominal walls following pregnancy[2]. Diagnosis can be confirmed...
by ultrasound or CT scan of the abdomen. The treatment of unilateral RSH is usually expectant and includes fluid resuscitation and blood transfusion. Surgical intervention or endovascular embolization of bleeding vessels is recommended in individuals with hemodynamic compromise. Bilateral RSH is extremely rare, and its causes are similar to those of unilateral RSH. However, its clinical manifestation is more serious and usually requires surgical or endovascular intervention[3-5].

Arterial embolization is a highly effective and safe method for treating bleeding from the abdomen and pelvis. The coaxial microcatheter technique to enable selective distal embolization of small vessel bleeding points at various sites throughout the body has been well described[6]. However, potential complications include failure to control bleeding radiologically or clinically, access site hematoma, contrast-induced nephropathy, spinal cord and peripheral nerve ischemia, and paraspinal muscle infarction or infection[7,8].

Reinitiation of anticoagulation after RSH appears to be controversial. A previous study showed that reinitiation of anticoagulants resulted in repeat bleeding in 5% of cases, and stated that reinitiated anticoagulation therapy appeared relatively safe[3]. However, we experienced a massive rebleed following reinitiation of anticoagulation therapy, and have some concerns about this suggestion. Therefore, guidelines specific to reinitiating anticoagulation are needed in the near future so that the risks and benefits of anticoagulation therapy following an RSH diagnosis can be carefully considered[3].

CONCLUSION
RSH should be suspected in patients who present with abdominal pain and abdominal mass, especially if they are elderly, female, or on anticoagulation therapy. Aggressive therapy, including intravascular embolization or surgery, could be required in cases of hemodynamic compromise. Anticoagulation after RSH should be restarted cautiously, after weighing the risks and benefits.

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Conflicts of Interest: None

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Case Report

A Dangerous Drug Combination for Emergency Service: Tarka®

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ABSTRACT

Calcium channel blocker poisoning is a common and sometimes life-threatening toxicity. Tarka is a combination antihypertensive medication composed of verapamil hydrochloride and trandolapril. Sinus bradycardia, severe hypotension, 2nd and 3rd degree atrioventricular (AV) blocks, cardiogenic shock and cardiac arrest can be seen due to excessive use of these drugs. In this study, we aim at discussing the case of a 13-year-old female patient in the light literature, who took 4 tablets of Tarka® forte tablets in order to commit suicide and reached our emergency department with sudden cardiac arrest and development of syncope. She was successfully resuscitated and given intravenous fluid and hyperinsulinemic/euglycemia therapy, epinephrine, vasopressor support, glucagon infusion and 6% hydroxyethyl starch support.

KEYWORDS: antihypertensive medication, calcium channel blocker, cardiac arrest, children, Tarka overdose

INTRODUCTION

In the present time, combined therapies are preferred rather than monotherapy in treatment of hypertension. One of the options for combined therapy is a combination of angiotensin converting enzyme inhibitors (ACEI) and calcium channel blockers[1,2]. Tarka® is a combination of antihypertensive drugs composed of trandolapril (4 mg) and verapamil hydrochloride (240 mg). The use of calcium channel blockers, being widely prescribed since the beginning of the 1990s, is one of the toxicity factors with a lethal progression due to the use of low doses in childhood[3]. In the last 15 years, incidence of accidental or intentional toxicity with high dose of calcium channel blockers (CCB) has increased by 30.6%[4]. It has been reported that 11,730 patients were referred to the hospital with a complaint of calcium channel toxicity in 2013 and 29 of these cases died in USA. Twelve percent of all the toxicity cases with this drug were in childhood age[5]. However, incidence of toxicity cases secondary to combination of trandolapril and verapamil hydrochloride reported in the childhood age in the literature is very low. In these papers, the reported lethal doses for verapamil and trandolapril were 720 - 1680 mg and 8 - 14 mg, respectively[6].

In this case presentation, our purpose was to draw the attention of the pediatric emergency physicians to the fact that intoxication cases caused by this drug combination is very rare, especially in childhood age, and that these cases may present several life-threatening features such as sudden cardiac arrest, renal failure, need for mechanical ventilation and severe hypotension.

CASE REPORT

The 13-year-old adolescent female patient was brought with complaints of syncope and confusion as referred from an external center to our emergency department. It was noted in her anamnesis that the patient was taken to an external medical center 8 hours before with findings of fatigue and somnolence after she used 4 pills of Tarka® (240 mg verapamil and 4 mg trandolapril) – currently being used as antihypertensive medication by her father - with an excuse of headache. Since no improvement occurred in her general condition in that external center, the patient was transferred to our emergency department with a complaint of syncope and confusion. On examination, the patient was found to have a pulse rate of 36 bpm, BP of 70/40 mmHg, and respiratory rate of 12 breaths per minute. She was given intravenous fluid and hyperinsulinemic/euglycemia therapy, epinephrine, vasopressor support, glucagon infusion and 6% hydroxyethyl starch support. She was successfully resuscitated and admitted to the intensive care unit for further monitoring.

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without any feature in her past medical history, was referred to our emergency department approximately 16 hours after ingestion of the drug.

Her physical examination revealed the following measurements: arterial tension: 60/30 mm Hg, heart rate: 62/min, respiration rate: 28/min and body temperature: 36 °C. She had moderate general condition, lethargic consciousness, body weight: 53 kg, length: 160 cm, 60/30 mm Hg and rhythmic breath sounds on auscultation. Neurological examination showed reduced deep tendon reflexes. The examination of other systems were normal.

**Laboratory tests results**: White blood cell count: 22,700/mm³, hemoglobin: 10.8 g/dL, platelets: 4,05,000/μL; creatine kinase (CK): 57 U/mL, CK-MB: 21 ng/mL (N: 0 - 3.23 ng/mL), Troponin-I: 4.1 ng/mL (N: 0 - 0.110 ng/mL), glucose: 414 mg/dL, creatinine: 2.09 mg/dL, blood urea nitrogen (BUN): 20 mg/dL, venous blood gas pH: 7.16, PCO₂: 49 mmHg, PO₂: 69 mmHg, HCO₃⁻: 17 mmol/L, BE: -11 mmol/L, SaO₂: 87%; aPTT: 22.2 sec, PT: 12.2 sec, INR: 1.1 and other biochemical levels encountered were normal. There were no additional findings except for bradycardia in her electrocardiography.

For hypotension, administration of dopamine and dobutamin was initiated by dosages of 10 μgr/kg/min and then increased up to 20 μgr/kg/min after loading 0.9% NaCl solution via 3 consecutive administrations of totally 20 cc/kg/dose. No improvement was found in bradycardia and hypotension in the patient and adrenaline infusion with dosage of 0.1 μgr/kg/min was added to treatment. The patient was administered CPR for 10 minutes because of sudden cardiac arrest during follow-ups and she was intubated and connected to the mechanical ventilator. The cardiac rhythm of the patient reverted back to normal and adrenaline infusion was increased gradually up to 1 μgr/kg/min. Arterial catheter was connected to the patient showing hypotensive course under mechanical ventilator and glucagon infusion was initiated. The patient, under clinical picture of shock, was loaded 6% hydroxyethyl starch (130/0.4) 500 cc. Hyperinsulinemia/euglycemia (HIE) therapy was initiated for accompanying hyperglycemia. Totally six ampoules of calcium were administered. The intubated patient was monitored and connected to mechanical ventilation. At the end of the 48th hour, infusions of dopamine, dobutamine and adrenaline were gradually decreased and stopped according to monitored findings of arterial blood pressure and pulse. Infusion of glucagon was stopped at the end of the 28th hour. The patient without hypotension, bradycardia, renal failure and hyperglycemia was transferred from the intensive care unit on the third day. The patient with improved clinical and laboratory findings was discharged due to recovery on the fourth day after admission.

**DISCUSSION**

Verapamil is a strong calcium channel blocker used primarily in the treatment of various cardiovascular diseases such as hypertension, cardiac arrhythmias and angina. Tarka® forte tablet includes 240 mg verapamil as an extended-release calcium channel blocker and 4 mg trandolapril as an immediate release ACE inhibitor. After metabolic conversion of verapamil to its active metabolite Norverapamil, it then reaches the peak plasma concentration in 4 - 15 hours. Norverapamil approximately shows 20% of the efficacy of verapamil. Most of verapamil and its metabolites (70%) are excreted by the kidneys. Trandolapril is a potent ACE inhibitor which decreases blood pressure by relaxing blood vessels mediated by inhibition of angiotensin II, a potent vasoconstrictor. Trandolaprilat, the major active metabolite of trandolapril is 8-fold more active than trandolapril and reaches peak plasma concentration in 2 - 12 hours. It is excreted by urinary and fecal excretion outside of the body.

The clinical findings usually appear 2 - 4 hours after ingestion of the medicine. This duration is 12 hours after for extended-release preparations and clinical findings may continue for 48 - 72 hours. Cases with hypotension longer than 24 hours and prolonged cardiac findings up to 7 days have been reported in the literature. Toxic dose of verapamil was found ranging between 800 mg to 24,000 mg when the reported cases were analyzed. Therapeutic blood concentration was reported ranging between 80 - 300 ng/ml while the range of lethal concentration was reported as 690 - 8800 ng/ml. Serious side effects usually occur to the cardiovascular system (CVS). Its action mechanism is monitored as decelerated transmission in the synoatrial and atrioventricular nodes and reduced inotropy. The most common clinical findings are hypotension and bradycardia. Other cardiac side effects include 2nd and 3rd degree AV block, cardiogenic shock and cardiac arrest. It has also been reported that changes in mental status, metabolic acidosis, hyperglycemia, persistent shock, hypokalemia, dizziness due to inadequate organ perfusion, seizure, stroke and acute respiratory distress syndrome (ARDS) also may be monitored in CCB intoxication. Probable action mechanism of death due to overdose ingestion of verapamil is based on reduced myocardial contractility or heart failure caused by cardiac block. The reported symptoms due to ACEI toxicity are hypotension, relative bradycardia, lethargy, eruption, anaphylaxia, coughing, drug fever, proteinuria, glomerulopathy, neutropenia, agranulocytosis, fatigue and impaired consciousness. The most serious side effects of trandolapril are severe angioedema and hypotension. The findings encountered in our patient were bradycardia, hypotension and cardiac arrest.
A very limited number of cases with intoxication due to high-dose ingestion of (Tarka®) verapamil and trandolaprilin were reported in the literature. Gokel et al[10-11] have presented two cases in which rhabdomyolysis vs thrombotic microangiopathy accompanied with acute renal failure developed 4 and 10 hours after administration of fixed-dose combination respectively. The first of those was a 28-year-old male patient who was referred with symptoms of serious hypotension and bradycardia 10 hours after taking 4 pills. The second patient was a 19-year-old female patient who was referred with symptoms of hypotension and bradycardia 4 hours after ingestion of 6 pills with suicidal intention and revealed anemia and thrombocytopenia in her followups. Batalis et al[6] have reported in their presented case of 4 pills that the patient died approximately 12 hours later due to Tarka® overdose and that toxicology report revealed a lethal verapamil level of 6000 ng/mL detected via autopsy and also indicated fatal circumstances such as renal failure which delayed elimination of both medicines. Cohen et al[3] have reported falling of a 60-year-old male patient due to dizziness after ingesting 5 pills of Tarka® and development of hypotension and bradycardia 8 hours later. Doğan et al[1] have reported a case of 3.5-year-old pediatric female case in whom worsening general condition and hypotension, hyperglycemia, leukocytosis, and development of A-V block 12 hours after ingestion of 6 tablets and insertion of a temporary pacemaker implantation in her therapy. Serious hypotension and bradycardia, renal failure, hyperglycemia and shock developed 16 hours after ingestion of 2 pills in our 13-year-old adolescent female case.

In the intoxication with fixed-dose combinations of antihypertensive drugs, lack of sufficient data and standardization on management of the patients lead to debates among physicians[4]. In hemodynamically unstable cases due to overdose of oral ingestion of Tarka®, airway, respiration and circulation should be primarily evaluated[1]. The treatment is based on decreasing drug absorption, supportive treatment and stabilization of cardiac functions. In such cases, administration of active charcoal is recommended within the first 1 hour after ingestion while it is suggested within the first 2 hours after ingestion of delayed-release pills. The administration of oral polyethylene glycol (PEG) and performing whole bowel irrigation are recommended for CCB intoxications due to ingestion of extended-release pills[12]. The use of PEG for sustained-release verapamil overdose has been recommended by Buckley et al reporting on three cases[13]. Cumpton and co-workers demonstrated that PEG should not be administered to hemodynamically unstable patients after sustained-release calcium channel blockers (CCB SR) overdose[14]. Hypotension may demonstrate resistance against treatment modalities. Regardless of the ingested dose, recovery of hypotension may take only several minutes or be prolonged until 24 hours[15]. Serious calcium channel blocker intoxications may be irresponsible against standard supportive treatments involving administration of IV fluids, atropine, catecholamines, cardiac pacing, and phosphodiesterase inhibitors such as calcium or milrinone[16]. Hypotension develops due to peripheral vasodilatation, reduced cardiac contractility, bradycardia or a combination of these circumstances[17]. The primary intervention in patients with hypotension should be replacement of the lacking volume by administration of crystalloid or colloid solutions[11]. Insufficient primary treatment and delayed hemodynamic stabilization are associated with increased risk of mortality[18]. According to the data obtained in recent years, most commonly used fluid for resuscitation is synthetic hydroxethyl starch (HES) from colloids. It has been emphasized in the clinical trials with small sample sizes conducted on HES solutions that they improve hemodynamic stabilization faster and that less amount of fluid is needed in retention of intravascular volume[19]. In our case, successful treatment was achieved via administration of 0.9% NaCl solution, sympathomimetic treatment, calcium, glucagon, insulin and HES. Our patient was seen 3 months after her discharge for control examination due to consideration for drug safety information related with the use of HES of The Turkish Medicines and Medical Devices Agency (TMMDA). It was reported that she had a complaint of persistent itching on lumbar region one week after her discharge which we have considered to be associated with use of HES. No findings were encountered in favor of renal deterioration in the follow-ups of renal functions.

Verapamil toxicity is found in a high number of studies in literature since most of the reports revealed mortality[6]. The most common clinical findings are hypotension and bradycardia. The other cardiac side effects include 2nd and 3rd degree AV block, cardiogenic shock and cardiac arrest[8]. On the other hand, it is stated that cardiac arrest due to Verapamil toxicity usually results in mortality[20]. In our case, cardiac arrest developed, CPR and adrenaline were administered. She was monitored for 28 hours as connected to mechanical ventilation in the intensive care unit and then transferred to the inpatient ward.

Hyperglycemia and metabolic acidosis are widely observed in cases of verapamil intoxications. Blockade on insulin release from the beta cells of the pancreatic islets and increased insulin resistance are considered as the primary reason for hyperglycemia. Potential metabolic acidosis that may occur in such cases is caused by elevated level of lactate due to hypoperfusion[6,21].

Levin et al.[21] have detected in their study that severity of intoxication due to overdose ingestion of CCB is positively correlated with hyperglycemia and that it is a good indicator in predicting clinical severity rather than hemodynamic impairment. HIE therapy and administration of glucagon are recommended since they recover cardiac inotropy and glucose metabolism. Patel et al.[22] have administered HIE therapy for 24 hours in a case where the patient ingested verapamil, captopril and glyburide and reported that HIE therapy is solely sufficient in stabilization of the patients. In our case, blood glucose levels decreased after HIE and glucagon therapy and glucagon therapy was stopped at the 28th hour. Also, there are publications which stated that some therapies such as intravenous lipid emulsion, intra aortic balloon pump, cardiopulmonary bypass, and extracorporeal membrane oxygenation (ECMO) are successful in the treatment of calcium channel blocker intoxication[66].

CONCLUSION

In conclusion, lack of a treatment protocol in cases of intoxication due to ingestion of combination drugs is an important problem. Although intoxication cases due to ingestion of Tarka are rare in pediatric patients, it may cause serious consequences such as renal failure, need for mechanical ventilation, hypotension and cardiac arrest. We conclude that 6% HES (130/0.4) can be administered for fluid resuscitation of hemodynamically unstable patients who are irresponsible to standard treatment protocols. However, large sample size prospective trials are needed to present this treatment as a strong recommendation. It should be kept in mind that even low doses of accidental or suicidal ingestion of verapamil may cause deaths.

REFERENCES

To the Editor

Diabetes mellitus has become one of the most significant public health threats of our time. In developed and developing countries alike, diabetes is now a leading cause of morbidity and mortality. With the rise of childhood obesity and sedentary lifestyles in many countries, diabetes is beginning to affect younger cohorts than ever before[1,2]. As the age at onset of type II diabetes mellitus (T2DM) falls, the health of women of reproductive age is being seriously challenged and adverse implications of pre-existing and gestational diabetes mellitus (GDM) for the pregnant woman, her foetus and new-born are becoming increasingly evident[3,4]. Despite this, many health systems have been slow to act on this issue.

Both pre-existing diabetes and GDM (which usually develops during the second or third trimester and typically subsides following delivery) can affect the health of the mother and child in a number of ways. Poorly managed pre-gestational diabetes, however, is thought to have the greater impact on the development of the fetus[5] since very early exposure to excess glucose can lead to disrupted neural tube development, and can cause cardiac abnormalities and severe neurological complications. Other outcomes such as musculoskeletal and genitor-urinary defects are also possible, and there is a significantly heightened risk of early miscarriage and associated maternal psychological trauma[6]. Observational studies further suggest that in pregnancies characterized by hyperglycemia, there is also a high risk of the child developing T2DM later in life[7,8]. In the case of GDM, there is also evidence that the mother’s risk of developing both GDM in future pregnancies and T2DM in later life is high.

The fact that many of the risks associated with diabetes during pregnancy can be limited and their impact mitigated by optimal glycaemic control[9], calls for more attention to be given to the prevention and management of diabetes as part of antenatal care services. Achieving normal glycaemic levels prior to pregnancy has been shown to reduce the risk of congenital malformations, first trimester miscarriages and other health issues[10], and counselling women on the risks of diabetes during pregnancy and working with them to ensure their blood glucose remains at optimal levels before conception, has been shown to improve pregnancy outcomes[11,12]. Since pregnancy is naturally associated with changes in insulin sensitivity, counselling is essential to ensuring that women know how pregnancy can affect diabetes treatment regimens and diabetes-associated complications. Neuropathy and retinopathy, for example, can worsen during pregnancy and require enhanced monitoring[13]. Certain common diabetes medications, moreover, such as angiotensin-converting enzyme (ACE) inhibitors, can increase the risk of fetal malformations[14].

Counselling is probably one of the most cost-effective interventions during the antenatal period, and in the specific case of diabetes, can positively impact the long-term health of both the mother and child. Despite this, pre-conception counselling continues to receive little attention, even among women known to have developed T2DM[15]. An Australian survey found that only 12% of pregnancies in women with T2DM had involved preconception counselling[15]. A recent study in Kuwait[16], where the prevalence of T2DM and GDM is on the rise, indicated that very limited counselling on GDM is provided in the primary health
care system, and that nurses and general practitioners are being substantially underutilised in this process.

Yet the antenatal period is typically a time when women and their partners are particularly open to advice on health issues. If this is taken advantage of, the benefits of pre-pregnancy counselling and better monitoring of pregnancies could be profound\cite{17}. Indeed, in some countries, calls have already been made for women known to have developed T2DM to be routinely provided with pre-pregnancy counselling for a period of at least three months, thus allowing them time to normalise their glycaemic control and begin taking recommended folic acid supplements\cite{18}. In most high-income countries, where antenatal services are likely to be well established, the addition of systematic counselling on themes such as glycaemic control, weight management and other steps that can be taken by women (and their partners) is long overdue. Nursing staff are ideally placed to do this, but in many settings, it may also be worthwhile to involve additional staff such as medical social workers, health educators and peer counsellors. This has been successfully tried in the area of breastfeeding promotion, and models from other fields of health care could easily be adapted to diabetes in pregnancy.

REFERENCES

Pesticide Knowledge and Safety Practices among Farm Workers in Kuwait: Results of a Survey

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The unsafe and indiscriminate use of pesticides in agriculture represents a major hazard to the environment and human health. The aim of this study was to assess the levels of knowledge, attitude and practices of Kuwaiti farmers regarding the safe use of pesticides. A total of 250 farmers participated in this study through in-depth interviews and observations on-farm. The majority of the farmers acknowledged that pesticides were harmful to their health (71%) and the environment (65%). However, farmers’ level of knowledge of pesticide safety is insufficient. Over 70% of the farmers did not read or follow pesticide label instructions, and 58% did not use any personal protective equipment (PPE) when handling pesticides. Educated farmers were significantly more likely to use PPE compared with farmers with limited formal education ($\chi^2 = 9.89$, $p < 0.05$). Storage of pesticides within living areas was reported by 20% of farmers. When disposing of pesticide wastes, respondents adopted unsafe practices such as discarding, incinerating, or burying empty pesticide containerson-farm, or reusing the containers. Farmers also reported disposing leftover pesticide solution or oldpesticide stocks on-farm or in the sewer. A significant number (82%) of the farmers reported at least one symptom of acute pesticide poisoning. Although farmers’ knowledge of pesticide hazards washigh, the reported safety measures were poor. Comprehensive intervention measures to reduce the health and environmental risks of pesticides are needed, including pesticide safety training programs for farmers, stringent enforcement of pesticide laws, and promoting integrated pest management and non-synthetic methods of pest control.

Segmental Arterial Mediolysis with 5 Splenic Artery Aneurysms. A Rare Finding of a Rare Disease: Case Report and Literature Review

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Introduction: Splenic artery aneurysms (SAA) are uncommon findings. They are usually single and isolated; however they can be multiple; hence vasculopathy and segmental artery mediolysis may be considered.

Presentation of Case: In our manuscript we present a case of a 54 year old multiparous lady who was discovered incidentally to have a diseased splenic artery containing five SSAs. The largest aneurysm
was close to the takeoff of the vessel and the smallest was distal embedded in the splenic hilum. Endovascular option was technically not feasible. Therefore the patient underwent a complete splenic artery resection with splenectomy and the histopathologic examination was suggestive of segmental arterial mediolysis (SAM).

**Discussion and Conclusion:** Multiple SAAs remains a rare finding of a rare disease. Complications can be crucial and high index of suspicion is important. Segmental arterial mediolysis can be considered in patients with several aneurysms on one anatomic site; Angiography is the gold standard diagnostic and therapeutic method. Complete splenic artery resection with splenectomy is the best treatment option for solitary vessel involvement.

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**Normal Reference Ranges for Pulmonary Artery Diameters in Preterm Infants**

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To establish normal reference ranges and Z-scores for pulmonary artery diameters in preterm infants and their correlation with body surface area, body weight, and chronological age. In a prospective study, 268 preterm infants, who fulfilled the inclusion criteria were examined. Echocardiograms were performed to measure the main pulmonary artery, right pulmonary artery, and left pulmonary artery diameters on day(s) 0 to -6 of life and at weekly intervals until they reached 36 weeks of age. Body surface area was divided into thirteen groups from 0.07 to 0.19 m². The mean gestational age was 29.8 (±2.38 SD) weeks, ranging between 24 and 35, the mean body weight was 1479 (±413 SD) grams, ranging between 588 and 3380, and the mean body surface area was 0.13 m², ranging between 0.07 and 0.19 m². All the pulmonary artery diameters correlated well with both body weight and body surface area. Reference ranges, with mean ± SD, range, and Z-scores for aortic diameters according to body surface area were calculated. A significant gradual increase was observed in main and branch pulmonary artery diameters with increasing body surface area. Overall, a progressive and significant increase for main and branch pulmonary artery diameters was observed during the first nine weeks of life. The main and branch pulmonary artery diameters were found to have significant correlation with body surface area. The study also provides reference data with Z-scores, which can be used as a normal reference tool for measuring the main pulmonary artery, right, and left pulmonary artery diameters of preterm infants against body surface area.

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**Brief Report: Social Support and Coping Strategies of Mothers of Children Suffering from ASD in Kuwait.**

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This cross-sectional study provides a general profile of mothers of children with ASDs in Kuwait and examines their use of social support resources and coping strategies (using the Brief COPE questionnaire).
The majority of mothers reported decreased ability to perform social duties (62.4%) and take care of themselves (50.5%). Overall, 57.7% of mothers reported a decreased ability to enjoy life; this difference was more pronounced among non-Kuwaiti mothers compared to Kuwaiti mothers (p value = 0.03), and in mothers with a bachelor’s degree or higher (p value = 0.011). There was a significant association between the mothers’ ability to enjoy life and receiving support from the family (p value = 0.021) and support groups (p value = 0.003). “Religion”, “Acceptance”, and “Positive Reframing” were the 3 most common coping strategies.

**Infant and young child feeding patterns in Kuwait: results of a cross-sectional survey**

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**Objective:** The beneficial role of breast-feeding for maternal and child health is now well established. Its possible role in helping to prevent diabetes and obesity in children in later life means that more attention must be given to understanding how patterns of infant feeding are changing. The present study describes breast-feeding profiles and associated factors in Kuwait.

**Design/Setting/Subjects:** Interviews with 1484 recent mothers were undertaken at immunisation clinics across Kuwait. Descriptive analysis and binary logistic regression of results were performed.

**Results:** Rates of breast-feeding initiation in Kuwait were high (98.1 %) but by the time of discharge from hospital, only 36.5 % of mothers were fully breast-feeding, 37.0 % were partially breast-feeding and 26.5 % were already fully formula-feeding. Multiple social and health reasons were given for weaning the child, with 87.6 % of mothers who had stopped breast-feeding completely doing so within 3 months postpartum. Nationality (P<0.001), employment status 6 months prior to delivery (P<0.001), mode of delivery (P=0.01), sex of the child (P=0.026) and breast-feeding information given by nurses (P=0.026) were all found to be significantly associated with breast-feeding. Few women (5.6 %) got information on infant nutrition and feeding from nursing staff, but those who did were 2.54 times more likely to be still breast-feeding at discharge from hospital. Over 70 % of mothers had enjoyed breast-feeding and 74 % said they would be very likely to breast-feed again.

**Conclusions:** In Kuwait where the prevalence of both obesity and type 2 diabetes is growing rapidly, the public health role of breast-feeding must be recognised and acted upon more than it has in the past.

**Antioxidant Supplements and Gastrointestinal Diseases: A Critical Appraisal.**

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The gastrointestinal tract digests and absorbs dietary nutrients, protects the body against physical and chemical damage from contents in its lumen, provides immunity against external antigens, and keeps an
Laparoscopic Sleeve Gastrectomy for the Management of Type 1 Diabetes Mellitus

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Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2017; 49 (3) : 271 - 280

4th International Conference on Parasitology
Sep 1 - 2, 2017
Czech Republic / Prague
Contact: Nidhi, Conferenceseries LLC
Phone: 650-353-9744
Email: parasitology@immunologyconferences.org

14th World Conference - Global Perspectives in Esophageal Diseases
Sep 2 - 5, 2017
Switzerland / Geneva
Contact: Congress Secretariat, Symporg SA
Phone: 011-41-22-839-8484
Email: oeso2017@symporg.ch

32nd International Congress on Epilepsy
Sep 2 - 6, 2017
Spain / Barcelona
Contact: Secretariat, International League against Epilepsy / International Bureau for Epilepsy
Phone: 011-353-1-205-6720
Email: barcelona@epilepsycongress.org

5th International Conference & Exhibition on Pain Research & Management
Sep 4 - 5, 2017
United Kingdom / London
Contact: Parimala Rayasam, Conferenceseries LLC
Phone: 702-508-8047
Email: painmanagemet2016@gmail.com

2nd International Conference on Anesthesia and Analgesia
Sep 7 - 8, 2017
United Kingdom / London
Contact: Conference Series.com
Email: anesthesia@surgeryconferences.org

6th International Congress on Lipid Metabolism & Atherosclerosis (ICOLA 2017)
Sep 8 - 9, 2017
South Korea / Seoul
Contact: Korean Society of Lipid and Atherosclerosis, Korean Society of Lipid and Atherosclerosis
Phone: +82-2-6203-1006
Email: icola2017master@gmail.com

12th Euro Global Gastroenterology Conference
Sep 11 - 12, 2017
France / Paris
Contact: Sophia Williams, Organizing Committee Assistant, Conference Series LLC
Phone: 702-508-5200
Email: gastrocongress@gastroconferences.com

18th International Conference on Alzheimer’s Drug Discovery
Sep 11 - 12, 2017
United States / New Jersey / Jersey City
Contact: Sara Classen, Assistant Director, Scientific Events, Alzheimer’s Drug Discovery Foundation
Phone: 212-901-8009
Email: sclassen@alzdiscovery.org

22nd International Conference on Cancer Drugs & Therapeutics
Sep 11 - 12, 2017
France / Paris
Contact: Pulsus Meetings
Phone: 234-567-8900

2nd International Conference & Expo on Optometry & Vision Science
Sep 11 - 12, 2017
France / Paris
Contact: Sam, Conferenceseries LLC
Phone: 702-508-5200
Email: optometry@ophthalmologyconferences.com

2017 European Congress of the International Society for the Study of Hypertension in Pregnancy (ISSHP)
Sep 6 - 9, 2017
Germany / Berlin
Contact: Mandy Wagner, Conventus Congressmanagement & Marketing GmbH
Phone: 011-49-36-4131-16160
Email: registrierung@conventus.de

18th Annual Asia-Pacific Association for Gynecologic Endoscopy & Minimally Invasive Therapy Congress
Sep 7 - 9, 2017
Japan / Okayama
Contact: Organizer, Japan Society of Gynecologic & Obstetric Endoscopy & Minimally Invasive Therapy
Phone: 011-81-6-6221-5933
Email: 18thapage2017@convention.co.jp
2nd International Conference on **Hypertension** & Healthcare
Sep 11 - 13, 2017
*Netherlands* / Amsterdam Cardiology
Contact: Jessie, Conference Series LLC
Phone: 702-508-9022
Email: hypertension@cardiologymeeting.com

47th Annual International **Continence** Society Meeting
Sep 12 - 15, 2017
*Italy* / Florence
Contact: Ella Siman, Kenes Group
Phone: 011-972-3-972-7967
Email: esiman@kenes.com

19th World Congress of International Society of **Cryosurgery** (ISC)
Sep 13 - 15, 2017
*Lithuania* / Kaunas
Contact: Greta Kazlauskaite, ISC Congress Secretariat
Phone: 011-370-686-44486
Email: ISC2017@eventas.lt

2017 International **Cancer** Education Conference
Sep 13 - 15, 2017
*United States* / Ohio / Cleveland
Contact: American Association for Cancer Education
Phone: 434-284-4445
Email: contactaace@aaceonline.com

10th International Meeting of **Pediatric Endocrinology**
Sep 14 - 17, 2017
*United States* / District of Columbia / Washington
Contact: Pediatric Endocrine Society
Phone: 703-556-9222
Email: info@pedsendo.org

11th International Symposium on **Antimicrobial Agents & Resistance** / 3rd International Interscience Conference on **Infection & Chemotherapy**
Sep 14 - 16, 2017
*South Korea* / Busan
Contact: Lorena Jeon, Ms., Asia Pacific Foundation for Infectious Diseases (APFID)
Phone: 011-82-2-3413-0327
Email: isaar-icic2017@apfid.org

1st Seha International Conference on Prevention and Control of **Infection**
Sep 14 - 15, 2017
*United Arab Emirates* / Abu Dhabi
Contact: Jerico, MENA Conference
Phone: 011-971-5-123-0727
Email: jerico@menaconference.com

7th World Congress on **Immunology**
Sep 14 - 16, 2017
*Netherlands* / Amsterdam Immunology/Allergy
Contact: Sareena Vani, Pulsus Meetings
Phone: 011-44-203-769-1765
Email: immunologyworld@cmesocietyconferences.com

Emerging **Antibiotic Resistance** in Gram-Negative Bacteria: Problems & Solutions
Sep 14 - 15, 2017
*Switzerland* / Fribourg
Contact: Thomas Greif, European Society of Clinical Microbiology & Infectious Diseases
Email: thomas.greif@escmid.org

World **Pathologists** Congress
Sep 14 - 15, 2017
*United States* / California / Los Angeles
Contact: Pulsus Meetings
Phone: 234-567-8900

11th Annual International **Liver Cancer** Association (ILCA) Conference
Sep 15 - 17, 2017
*South Korea* / Seoul
Contact: ILCA
Phone: 011-32-2-789-2345
Email: info@ilca-online.org

3rd International Conference on New Concepts in **Lymphoid Malignancies**: Focus On Cll & Indolent Lymphoma
Sep 15 - 17, 2017
*France* / Cannes
Contact: Ghyslaine Lebougault, Manager, European School of Haematology
Phone: 011-33-1-5727-6739
Email: ghyslaine.lebougault@univ-paris-diderot.fr

6th International Society for **Pharmacoeconomics** & Outcomes Research (ISPOR) Latin America Conference
Sep 15 - 17, 2017
*Brazil* / Sao Paulo
Contact: Meetings Department, ISPOR
Email: meetingsinfo@ispor.org

Advanced Musculoskeletal MRI: **Arthritis** & Beyond
Sep 15 - 17, 2017
*China* / Hangzhou
Contact: Melisa, Meetings Coordinator, International Society for Magnetic Resonance in Medicine
Phone: 510-841-1899
Email: melisa@ismrm.org
Essentials in Fetal MRI: Methods and Brain Imaging
Sep 15, 2017
Austria / Vienna
Contact: International Society of Ultrasound in Obstetrics & Gynecology
Phone: 011-44-20-7471-9955
Email: info@isuog.org

Modern Obstetric Management: The Latest Updates
Sep 15, 2017
Austria / Vienna
Contact: International Society of Ultrasound in Obstetrics & Gynecology
Phone: 011-44-20-7471-9955
Email: info@isuog.org

16th Human Proteome Organisation World Conference
Sep 17 – 21, 2017
Ireland / Dublin
Contact: Aine Mitchell, Ms, Conference Partners
Phone: 011-35-31-296-8688
Email: HUPO2017@conferencepartners.ie

3rd International Congress on Microbiology
Sep 18 - 19, 2017
United States / Arizona / Phoenix
Contact: Pulsus Meetings
Phone: 234-567-8900

46th World Congress on Microbiology
Sep 18 - 19, 2017
Ireland / Dublin
Contact: Conference Series.com
Email: microbiology@conferenceseries.com

International Conference on Viral Infections, Outbreaks, Ebola & Control
Sep 18 - 20, 2017
United States / Texas / Dallas
Contact: Pulsus Meetings
Phone: 234-567-8900

World Congress on Cognitive Behavioural Science and Therapy
Sep 18 - 20, 2017
United States / Texas / San Antonio
Contact: Pulsus Meetings
Phone: 234-567-8900
Email: wcbt@cmesocietyconferences.com

World Dermatological Congress
Sep 18 - 20, 2017
United States / Texas / San Antonio
Contact: Pulsus Meetings
Phone: 234-567-8900
Email: dermatologycongress@conferenceseries.com

2nd International Conference on Pediatric Acquired Brain Injury
Sep 20 - 23, 2017
Italy / Rome
Contact: Colleen LoGrande, International Brain Injury Association
Email: clogrande@internationalbrain.org

3rd International Conference on Advanced Clinical Research & Clinical Trials
Sep 20 - 21, 2017
Ireland / Dublin
Contact: Conference Series.com
Email: clinicalresearch@pharmaceuticalconferences.org

Shaping the Future of Pediatrics
Sep 20 – 22, 2017
Italy / Rome
Contact: Vittoria Paolini, MCA Scientific Events
Phone: +39-2-3493-4404
Email: paolini@mcascientificevents.eu

1st International Congress of the World Association for Psychosocial Rehabilitation
Sep 21 - 23, 2017
United Arab Emirates / Abu Dhabi
Contact: Afsal Ahmad, Mena Conference
Phone: 011-971-2-491-9888
Email: afsal.ahmad@menaconf.com

2017 International Conference on Diabetes and Healthcare
Sep 21 - 23, 2017
United States / Texas / Houston
Contact: Olivia Smith, Diabetes 2017 Program Manager, Pulsus Meetings
Phone: 011-44-20-3769-1765
Email: diabetes@cmesocietyconferences.com

2017 Tissue Engineering & Regenerative Medicine
International Society (TERMIS) Asia Pacific Conference
Sep 21 - 24, 2017
China / Nantong
Contact: Sarah Wilburn, TERMIS Administrator, TERMIS
Phone: 925-362-0998
Email: swilburn@termis.org

22nd International Summit on Violence, Abuse & Trauma
Sep 21 - 27, 2017
United States / California / San Diego
Contact: Institute on Violence, Abuse & Trauma
Phone: 858-527-1860
2nd Middle East International Dermatology & Aesthetic Medicine Conference & Exhibition  
Sep 21 - 23, 2017  
United Arab Emirates / Dubai  
Contact: Epin Kurra, Manager, InfoPlus Events 
Phone: +971-4-421-8996  
Email: MEIDAM@InfoPlusEvents.com

International Conference and Expo on Heart Surgery  
Sep 21 – 22, 2017  
United States / Texas / San Antonio  
Contact: Pulsus Meetings  
Phone: 234-567-8900

International Conference on Clinical & Medical Genetics  
Sep 21 – 22, 2017  
Canada / Ontario / Toronto  
Contact: Conference Series.com  
Email: clinicalgenetics@geneticsmeetings.com

International Conference on Osteoporosis, Arthritis & Musculoskeletal Disorders  
Sep 21 – 22, 2017  
Spain / Madrid  
Contact: Pulsus Meetings  
Phone: 234-567-8900  
Email: osteoporosis@cmesocietyconferences.com

Pancreas Workshop: A Multidisciplinary Imaging Approach  
Sep 21 - 22, 2017  
Sweden / Stockholm  
Contact: European Society of Gastrointestinal & Abdominal Radiology Office  
Phone: 011-43-1-535-8927  
Email: office@esgar.org

7th International Arab Neonatal Care Conference  
Sep 27 - 30, 2017  
United Arab Emirates / Dubai  
Contact: Mohammed Said, Manager, Blueocean Event Management  
Phone: 011-971-4450-2485  
Email: info@blueocean-me.com

24th Annual Middle East Fertility Society (MEFS) Scientific Meeting  
Sep 28 - 30, 2017  
United Arab Emirates / Dubai  
Contact: Congress Secretariat, MEFS  
Phone: 011-961-1-610-400  
Email: registration@mefs.org

37th Annual International Cardiothoracic Surgery Symposium (CREF)  
Sep 28 - Oct 1, 2017  
United States / California / San Diego  
Contact: CREF  
Phone: 805-541-3118  
Email: info@crefmeeting.com

38th International Society of Dermatopathology Symposium  
Sep 28 - 30, 2017  
United Kingdom / Glasgow  
Contact: British Association of Dermatologists  
Phone: 011-44-20-7391-6072  
Email: conference@bad.org.uk

3rd Mena Orthopaedic Congress  
Sep 28 - 30, 2017  
United Arab Emirates / Dubai  
Contact: Sara Ahmed, Maarefah Management  
Email: sara.k@maarefah-management.org

Galen Advanced Course on Cardio-Thoracic Cross-Sectional Imaging  
Sep 28 - 29, 2017  
Germany / Heidelberg  
Contact: European School of Radiology  
Phone: 011-43-1-533-406-4535  
Email: esor@myESR.org

International Cartilage Repair Society Focus Meeting: Osteoarthritis in Athletes  
Sep 28 - 29, 2017  
Switzerland / Zurich  
Contact: Melanie Twerenbold, Organizer, Cartilage Executive Office GmbH  
Phone: 011-41-44-503-7370  
Email: office@cartilage.org

2nd Annual Pituitary Disease Conference: Case-Based Management  
Sep 29, 2017  
United Arab Emirates / Abu Dhabi  
Contact: Conference Secretariat, Meeting Minds Experts  
Phone: 011-971-4-427-0492  
Email: pdc@meetingmindsexperts.com

Introduction to Rare Movement Disorders Diseases  
Sep 29 - 30, 2017  
Uruguay / Montevideo  
Contact: International Secretariat, International Parkinson & Movement Disorder Society  
Phone: 414-276-2145  
Email: info@movementdisorders.org
Forthcoming Conferences and Meetings

Point Of Care Testing Advances Conference
Sep 30, 2017
United Arab Emirates / Abu Dhabi
Contact: POCT Advances Conference Secretariat, Meeting Minds Experts
Phone: 011-971-4-427-0492
Email: poctadvances@meetingmindsexperts.com

1st Middle East School for Young Neurologists
Oct 2 - 3, 2017
Kuwait / Kuwait
Contact: International Secretariat, International Parkinson & Movement Disorder Society
Phone: 414-276-2145
Email: info@movementdisorders.org

5th International Conference & Exhibition on Pain Research & Management
Oct 2 - 3, 2017
United Kingdom / London
Contact: Conference Series.com
Email: painmanagement@conferenceseries.com

World Summit on Reproductive Biology and Medicine
Oct 5 - 6, 2017
Georgia / Atlanta
Contact: Pulsus Meetings
Phone: 234-567-8900
Email: reproductivebiology@cmesocietyconferences.com

45th Annual Meeting of the International Society for Pediatric Neurosurgery
Oct 8 - 12, 2017
United States / Colorado / Denver
Contact: Evren Ertan, Kenes Turkey
Phone: 011-41-22-908-0488
Email: eertan@kenes.com

16th International Conference on Neuro Cognitive Disorders
Oct 9 - 10, 2017
United Kingdom / London
Contact: Conference Series.com
Email: neurocognitive@neuroconferences.com

2017 International Conference on Viral Hepatitis
Oct 9 - 10, 2017
United States / Illinois / Chicago
Contact: International Association of Providers of AIDS Care
Phone: 202-507-5899
Email: iapac@iapac.org

11th International Congress on Toxicology and Risk Management
Oct 10 - 12, 2017
United Kingdom / London
Contact: Conference Series.com
Email: global@toxicologyconferences.org

2017 World Vaccine Congress
Oct 10 - 12, 2017
Spain / Barcelona
Contact: Ina Luft, Terrapinn
Phone: 011-44-20-7092-1191
Email: ina.luft@terrapinn.com

Immune Profiling World Congress
Oct 10 - 12, 2017
Spain / Barcelona
Contact: Ina Luft, Terrapinn
Phone: 011-44-20-7092-1191
Email: Ina.Luft@terrapinn.com

3rd World Congress on Abdominal & Pelvic Pain
Oct 11 - 15, 2017
United States / District Of Columbia / Washington
Contact: International Pelvic Pain Society Executive Office
Phone: 847-517-8712
Email: info@pelvicpain.org

19th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology & Therapy
Oct 12 - 15, 2017
Portugal / Estoril
Contact: Ghyslaine Lebougault, Manager, European School of Haematology
Phone: 011-33-1-5727-6739
Email: ghyslaine.lebougault@univ-paris-diderot.fr

49th Congress of the International Society of Paediatric Oncology
Oct 12 - 15, 2017
United States / District of Columbia / Washington
Contact: SIOP Secretariat, Kenes International
Email: siop@kenes.com

5th International Oncology Conference
Oct 12 - 13, 2017
United Arab Emirates / Abu Dhabi
Contact: Afsal Ahmad, Mena Conference
Phone: 011-971-2-491-9888
Email: afsal.ahmad@menaconf.com

1st Annual European Congress on Breast Cancer™
Oct 13 - 14, 2017
France / Paris
Contact: Physicians’ Education Resource, LLC
Phone: 609-378-3701
Email: info@gotoper.com
2017 Map – Molecular Analysis for Personalised Therapy
Oct 13 - 14, 2017
Switzerland / Zurich
Contact: Overcome
Phone: 011-33-1-4192-0127
Email: map@overcome.eu

10th World Congress on Developmental Origins of Health & Disease
Oct 15 - 18, 2017
Netherlands / Rotterdam
Contact: Sylvie van den Assum, Erasmus MC
Email: dohad.2017@erasmusmc.nl

12th International Congress on Innovations in Coronary Artery Disease
Oct 15 - 17, 2017
Italy / Venice
Contact: Sarah Krein, Paragon Group
Phone: 011-41-22-533-0948
Email: skrein@paragong.com

18th World Conference on Lung Cancer
Oct 15 - 18, 2017
Japan / Yokohama
Contact: International Conference Services Ltd.
Phone: 604-681-2153
Email: info@icsevents.com

2017 Global Summit on Gastroenterology
Oct 16 - 18, 2017
United Arab Emirates / Dubai
Contact: Mack Aidan, Gastro 2017, Scientific Future Group
Phone: 011-91-040-4018-0961
Email: secretary@gastrocongress.com

15th World Medical Nanotechnology Congress & Expo
Oct 18 - 19, 2017
Japan / Osaka
Contact: Conference Series.com
Email: medicalnano@nanotechconferences.org

43rd Annual Conference of the International Society for Pediatric & Adolescent Diabetes
Oct 18 – 21, 2017
Austria / Innsbruck
Contact: Conference Secretariat, K.I.T. Group GmbH
Phone: 011-49-30-2460-3270
Email: registration-ispad2017@kit-group.org

9th World Congress of Melanoma / 14th International Congress of the Society for Melanoma Research
Oct 18 - 21, 2017
Australia / Brisbane
Contact: MCI Deutschland GmbH
Phone: 011-49-30-204-590
Email: congress@worldmelanoma2017.com

2017 World Oncology Forum
Oct 19 - 21, 2017
Switzerland / Lugano
Contact: European School of Oncology
Phone: 011-39-2-854-6451
Email: eso@eso.net

25th World Cancer Conference
Oct 19 - 21, 2017
Italy / Rome
Contact: Conference Series.com
Email: worldcancer@conferenceseries.net

14th Global Obesity Meeting
Oct 23 - 24, 2017
United Arab Emirates / Dubai
Contact: Srija, Conferenceseries LLC
Phone: 650-889-4686 ext. 6092
Email: obesitymeeting@obesityconference.org

World Molecular Biology and R&D Summit
Oct 23 - 24, 2017
Canada / Ontario / Toronto
Contact: Richard Matthew, Molecular biology 2017, Allied Academies
Phone: 828-214-3944
Email: molecularbiology@alliedconferences.org

13th Patient Safety Conference and Exhibition
Oct 24 - 26, 2017
United Arab Emirates / Dubai
Contact: Rejoy Penacerrada, Conference Producer, Informa Life Sciences Exhibitions
Phone: +971-4-407-2488
Email: rejoy.penacerrada@informa.com

56th International Spinal Cord Society Annual Scientific Meeting
Oct 24 - 26, 2017
Ireland / Dublin
Contact: Zibrant
Email: iscos2017@zibrant.com

2017 Dubai Nutrition Conference
Oct 26 - 28, 2017
United Arab Emirates / Dubai
Contact: Kris Olarte, Marketing Executive, MCI Dubai
Phone: 011-971-4-311-6300
Email: kris.olarte@mci-group.com
Forthcoming Conferences and Meetings

Oct 26 - 29, 2017
United Arab Emirates / Abu Dhabi
Contact: Nida Nafis, MCI Middle East
Phone: 011-971-4-311-6300
Email: isam@mci-group.com

2017 Lymphoma & Meyloma: An International Congress on Hematologic Malignancies
Oct 26 - 28, 2017
United States / New York / New York
Contact: Imedex
Phone: 770-751-7332; Fax: 770-751-7334
Email: meetings@imedex.com

11th Men's Health World Congress
Oct 27 - 29, 2017
Italy / Florence
Contact: Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140

15th International Conference on Obesity Medicine
Oct 30 - Nov 1, 2017
Thailand / Bangkok
Contact: Keerthi, Mrs, Conferenceseres LLC
Phone: 650-889-4686
Email: obesitymedicine@obesityconference.org

2017 International Virology Conference
Oct 30 – 31, 2017
Canada / Ontario / Toronto
Contact: Tobias, International Virology Conference, Allied Academies
Phone: 828-214-3944
Email: virologyconference@alliedconferences.org

2nd International Conference on Worldwide Infectious Diseases
Oct 30 – 31, 2017
United States / Georgia / Atlanta
Contact: Pulsus Meetings
Phone: 234-567-8900

3rd International Conference on Transcriptomics
Oct 30 - Nov 1, 2017
Thailand / Bangkok
Contact: John, Program Manager, Conference Series
Phone: 800-216-6499
Email: transcriptomics@biochemconferences.org

2017 World Immunotherapy Congress
Oct 31 - Nov 2, 2017
Switzerland / Basel
Contact: Aurore Colella, Terrapinn
Phone: 011-44-20-7092-1178
Email: aurore.colella@terrapinn.com

2017 International Conference on Embryology
Nov 2 - 3, 2017
United States / Illinois / Chicago
Contact: Alicia, Embryology 2017, Allied Academies
Phone: 800-858-2189
Email: aliciawilliam@rediffmail.com

Antibiotic Therapy in Practice
Nov 2 - 4, 2017
Spain / Madrid
Contact: Thomas Greif, European Society of Clinical Microbiology & Infectious Diseases
Email: thomas.greif@escmid.org

Selected Topics in Craniomaxillofacial Surgery: An International Symposium on Cranioplasty & Implantable Neurotechnology
Nov 3 - 5, 2017
United States / Massachusetts / Boston
Contact: Johns Hopkins Medicine
Phone: 410-955-2959
Email: cmenet@jhmi.edu

20th Annual International Society for Pharmacoeconomics & Outcomes Research (ISPOR) European Congress
Nov 4 - 8, 2017
United Kingdom / Glasgow
Contact: Meetings Department, ISPOR
Email: meetingsinfo@ispor.org

2017 Annual Radiology Meeting in UAE
Nov 5 - 7, 2017
United Arab Emirates / Dubai
Contact: Coline Monsarrat, Sales Business Development, Index Conferences & Exhibition
Phone: 011-971-5-2344-2840
Email: coline.monsarrat@index.ae

2017 National Cancer Research Institute (NCRI) Cancer Conference
Nov 5 - 8, 2017
United Kingdom / Liverpool
Contact: NCRI Executive
Phone: 011-44-20-3469-5453
Email: ncrcconference@ncri.org.uk

12th Global Dermatologists Conference
Nov 6 - 7, 2017
United Kingdom / London
Contact: Richard Parker, Program Manager, Conference series LLC
Phone: 702-508-5201
Email: dermatologists@dermatologymeeting.com
2017 Aortic International Conference on Cancer in Africa
Nov 7 - 10, 2017
Rwanda / Kigali
Contact: AORTIC Conference Secretariat, African Agenda
Phone: 011-27-21-683-2934
Email: info@aorticconference.org

6th Emirates International Urological Conference & 28th World Congress on Video-Urology & Advances in Clinical Urology
Nov 8 - 11, 2017
United Arab Emirates / Abu Dhabi
Contact: Secretariat, Meeting Minds EXPERTS
Phone: +971-4-427-0492
Email: eusc@meetingmindsexperts.com

2017 International Society of Geriatric Oncology (SIOG) Annual Conference
Nov 9 - 11, 2017
Poland / Warsaw
Contact: SIOG Administrative Office
Phone: 011-41-22-552-3305
Email: info@siog.org

2017 International Symposium on Molecular Allergology
Nov 9 - 11, 2017
Luxembourg / Luxembourg
Contact: European Academy of Allergy & Clinical Immunology Headquarters
Phone: 011-41-44-205-5533
Email: events@eaaci.org

33rd Annual International Society for Traumatic Stress Studies (ISTSS) Meeting: Trauma & Complexity - From Self to Cells
Nov 9 - 11, 2017
United States / Illinois / Chicago
Contact: ISTSS
Phone: 847-686-2234; Fax: 847-686-2251
Email: info@istss.org

3rd Annual International Heart Failure Conference
Nov 9 - 10, 2017
United Arab Emirates / Abu Dhabi
Contact: Afsal Ahmad, Mena Conference
Phone: 011-971-2-491-9888
Email: afsal.ahmad@menaconf.com

22nd World Congress on Parkinson’s Disease & Related Disorders
Nov 12 - 15, 2017
Vietnam / Ho Chi Minh City
Contact: Severine Schindele, INTERPLAN AG
Phone: 011-49-40-325-092 ext. 30
Email: iaprd@interplan.de

11th International Congress on Early Onset Scoliosis
Nov 16 - 17, 2017
United States / California / San Diego
Contact: Growing Spine Foundation
Phone: 414-276-6445
Email: info@growingspine.org

3rd Annual Mena Women’s Health Congress
Nov 16 - 18, 2017
United Arab Emirates / Dubai
Contact: Maarefah Management, Maarefah Management
Email: info@pediaortho.com

5th GCC and 5th Emirates International Neurosurgical Conference
Nov 16 - 18, 2017
United Arab Emirates / Dubai
Contact: Mohamed Refaat, Meeting Minds Experts
Phone: 011-971-55-938-1332
Email: mohamed@meetingmindsdubai.com

2017 Emirates Dermatology Society Annual Conference
Nov 17 - 19, 2017
United Arab Emirates / Abu Dhabi
Contact: Organizer, K.I.T. Group Middle East FZ LLC
Phone: 011-971-2-245-0057
Email: info@edsuae.com

3rd Advanced Medicine Congress
Nov 17-18, 2017
United Arab Emirates / Abu Dhabi
Contact: Darren Eletr, Marketing Communications Coordinator, Imperial College London Diabetes Centre
Phone: +971-3-746-4848
Email: deletr@icldc.ae

6th International Conference on Medical Cannabis & Cannabinoids
Nov 22 - 24, 2017
Czech Republic / Prague
Contact: Josh Margo, Mr, Kenes Group
Phone: 011-972-3-972-7450
Email: jmargo@kenes.com

3rd Middle East North Africa Committee for Research & Treatment in Multiple Sclerosis (Menactrims) Congress
Nov 24 - 25, 2017
United Arab Emirates / Dubai
Contact: Basil Kadara, General Manager, DiaEdu Management Consultants
Phone: +971-4-453-2975
Email: contact@diaedu.com
<table>
<thead>
<tr>
<th>Conference</th>
<th>Date</th>
<th>Location</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; International Conference on <strong>Medicine, Internal Medicine, Dentistry, Pharmacology, Nursing &amp; Healthcare</strong></td>
<td>Nov 25 - 26, 2017</td>
<td><strong>Turkey</strong> / Istanbul</td>
<td>Seval, Coordinator, Scientific Cooperations, Phone: 011-90-312-223-5570, Email: <a href="mailto:secretary@med-scoop.org">secretary@med-scoop.org</a></td>
</tr>
<tr>
<td>2017 International Federation for <strong>Adipose Therapeutics and Science</strong> (IFATS) Meeting</td>
<td>Nov 30 - Dec 3, 2017</td>
<td><strong>United States</strong> / Florida / Miami</td>
<td>IFATS Executive Office, Phone: 603-643-2325, Fax: 603-643-1444</td>
</tr>
<tr>
<td>25&lt;sup&gt;th&lt;/sup&gt; World Congress on Controversies in <strong>Obstetrics, Gynecology &amp; Infertility</strong></td>
<td>Nov 30 - Dec 2, 2017</td>
<td><strong>Austria</strong> / Vienna</td>
<td>Ilana Rabinoff-Sofer, CongressMed, Phone: 011-41-22-339-9985, Email: <a href="mailto:cogi@congressmed.com">cogi@congressmed.com</a></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Gulf International <strong>Neonatology</strong> Quality Conference</td>
<td>Dec 1 – 2, 2017</td>
<td><strong>Oman</strong> / Muscat</td>
<td>Mohammed Said, Manager, Blueocean Events management, Phone: 011-971-4-450-2485, Email: <a href="mailto:info@blueocean-me.com">info@blueocean-me.com</a></td>
</tr>
<tr>
<td>2017 World <strong>Diabetes</strong> Congress</td>
<td>Dec 4 - 8, 2017</td>
<td><strong>United Arab Emirates</strong> / Abu Dhabi</td>
<td>Congress Secretariat, International Diabetes Federation, Phone: 011-32-2-543-1631, Email: <a href="mailto:wdc@idf.org">wdc@idf.org</a></td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; International Conference on <strong>Clinical Microbiology</strong></td>
<td>Dec 4 - 5, 2017</td>
<td><strong>United States</strong> / Texas / Dallas</td>
<td>Pulsus Meetings, Phone: 234-567-8900</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; International Conference on <strong>Neurorehabilitation</strong></td>
<td>Dec 4 - 6, 2017</td>
<td><strong>United States</strong> / Texas / Dallas</td>
<td>Pulsus Meetings, Phone: 234-567-8900, Email: <a href="mailto:neurorehabilitation@cmesociety.com">neurorehabilitation@cmesociety.com</a></td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt; Annual Bit World Congress of <strong>Geriatrics and Gerontology</strong></td>
<td>Dec 4 - 6, 2017</td>
<td><strong>Japan</strong> / Fukuoka</td>
<td>Ms. Julia, Program Coordinator, BIT Group Global Ltd., Phone: 011-86-411-8479-9609, Email: <a href="mailto:julia@wcgg-bit.com">julia@wcgg-bit.com</a></td>
</tr>
<tr>
<td>International <strong>Heart</strong> Conference</td>
<td>Dec 4 - 5, 2017</td>
<td><strong>United States</strong> / Texas / Dallas</td>
<td>Pulsus Meetings, Phone: 234-567-8900, Email: <a href="mailto:heart@cmesociety.com">heart@cmesociety.com</a></td>
</tr>
<tr>
<td>2017 Emirates Society of <strong>Emergency Medicine</strong> Conference</td>
<td>Dec 6 - 9, 2017</td>
<td><strong>United Arab Emirates</strong> / Dubai</td>
<td>Kris Olarte, Marketing Executive, MCI Middle East, Phone: 011-971-4-311-6300, Email: <a href="mailto:kris.olarte@mci-group.com">kris.olarte@mci-group.com</a></td>
</tr>
<tr>
<td>13&lt;sup&gt;th&lt;/sup&gt; International Conference on <strong>Clinical Gastroenterology &amp; Hepatology</strong></td>
<td>Dec 7 - 8, 2017</td>
<td><strong>Spain</strong> / Madrid</td>
<td>Alexander Lee, Project Manager, Pulsus Meetings, Phone: 702-508-5200, Email: <a href="mailto:clinicalgastro@gastroenterologysociety.org">clinicalgastro@gastroenterologysociety.org</a></td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt; Annual Gulf <strong>Obesity Surgery</strong> Society Meeting</td>
<td>Dec 7 - 9, 2017</td>
<td><strong>United Arab Emirates</strong> / Dubai</td>
<td>Nida, Marketing Executive, MCI Dubai, Phone: 011-971-4-311-6300, Email: <a href="mailto:nida.nafis@mci-group.com">nida.nafis@mci-group.com</a></td>
</tr>
<tr>
<td>22&lt;sup&gt;nd&lt;/sup&gt; World <strong>Cardiology</strong> Conference</td>
<td>Dec 11 - 12, 2017</td>
<td><strong>Italy</strong> / Rome</td>
<td>Ellena Stewart, Program Coordinator, Conference Series.com, Phone: 702-508-5200 ext: 8033, Email: <a href="mailto:worldcardiology@conferenceseries.net">worldcardiology@conferenceseries.net</a></td>
</tr>
<tr>
<td>2017 Gulf PCR Middle-Eastern <strong>Cardiovascular</strong> Course</td>
<td>Dec 13 - 14, 2017</td>
<td><strong>United Arab Emirates</strong> / Dubai</td>
<td>Rima Salama, Registration, Europa Organisation, Phone: 011-33-5-3445-2645, Email: <a href="mailto:gulfpcr@europa-organisation.com">gulfpcr@europa-organisation.com</a></td>
</tr>
</tbody>
</table>
3rd Emirates Surgical Pathology Conference (ESPC 2017) 
Dec 14 - 16, 2017 
United Arab Emirates / Dubai 
Contact: Conference Secretariat, Meeting Minds Experts 
Phone: +971-4-427-0492 
Email: espc@meetingmindsexperts.com 

2nd Annual International Congress on Immunotherapies in Cancer™: Focus On Practice-Changing Application 
Dec 16, 2017 
United States / New York / New York 
Contact: Physicians’ Education Resource, LLC 
Phone: 609-378-3701 
Email: info@gotoper.com 

6th International Congress of the Emirates Neurology Society 
Jan 12 - 13, 2018 
United Arab Emirates / Dubai 
Contact: Basil Kadara, General Manager, DiaEdu Management Consultants 
Phone: +971-4-453-2975 
Email: sara@diaedu.com 

8th Emirates Otorhinolaryngology Audiology & Communication Disorders Congress 
Jan 17 - 19, 2018 
United Arab Emirates / Dubai 
Contact: Nida, Marketing Executive, MCI Dubai 
Phone: 011-971-4-311-6300 
Email: nida.nafis@mci-group.com 

2018 International Stroke Conference 
Jan 24 - 26, 2018 
United States / California / Los Angeles 
Contact: Convention Data Services 
Fax: 508-743-9607 
Email: InternationalStroke@xpressreg.net 

2018 Gulf Arrhythmia Congress 
Jan 25 - 27, 2018 
United Arab Emirates / Dubai 
Contact: Basil Kadara, General Manager, DiaEdu Management Consultants 
Phone: +971-4-453-2975 
Email: sara@diaedu.com 

20th International Conference on Dialysis - Advances In Kidney Disease 
Jan 31 - Feb 2, 2018 
United States / Florida / Lake Buena Vista 
Contact: Crystal Johnson, Renal Research Institute 
Phone: 212-331-1700 
Fax: 212-331-1701 
Email: crystal.johnson@rriny.com 

1st International Congress of Hypertension in Children and Adolescents 
Feb 9 - 11, 2018 
Spain / Valencia 
Contact: Sarah Krein, Paragon Group 
Phone: +41-22-533-0948 
Email: skrein@paragon.com 

4th International 4 Corners of Cardiology Meeting 
Feb 9 - 10, 2018 
Australia / Melbourne 
Contact: Meeting Manager, Arinex Pty Ltd 
Phone: 011-61-3-9417-0888 
Email: 4ccardiology@arinex.com.au 

11th International Conference on Advanced Technologies & Treatments for Diabetes 
Feb 14 - 17, 2018 
Austria / Vienna 
Contact: Ella Siman, Kenes Group 
Phone: 011-41-22-908-0488 
Email: esiman@kenes.com 

21st Joint Meeting of the International Society of Dermatopathology (ISDP) 
Feb 14 - 15, 2018 
United States / California / San Diego 
Contact: Diana Baughman, Manager, ISDP 
Phone: 650-726-5481 

46th Annual International Neuropsychological Society (INS) Meeting 
Feb 14 - 17, 2018 
United States / District Of Columbia / Washington 
Contact: INS 
Phone: 801-487-0475 
Email: INS@utah.edu 

5th International Conference on Prehypertension, Hypertension & Cardio Metabolic Syndrome 
Feb 22 - 25, 2018 
Italy / Venice 
Contact: Liat Halevy, Secretariat, Paragon Group 
Phone: +41-22-533-0948 
Email: secretariat@prehypertension.org 

2018 World Psychiatric Association Thematic Congress 
Feb 25 - 28, 2018 
Australia / Melbourne 
Contact: Ron Marcovici, Kenes Group 
Phone: 011-41-22-908-0488 
Email: rmarcovici@kenes.com
WHO-Facts Sheet

1. Lassa Fever
2. Rift Valley Fever
3. Oral Health
4. Autism Spectrum Disorders
5. Chronic Obstructive Pulmonary Disease (COPD)

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2017; 49 (3) : 281 - 290

1. LASSA FEVER

Overview

Lassa fever is a zoonotic disease, meaning that humans become infected from contact with infected animals. The animal reservoir, or host, of Lassa virus is a rodent of the genus Mastomys, commonly known as the “multimammate rat.” Mastomys rats infected with Lassa virus do not become ill, but they can shed the virus in their urine and faeces.

Because the clinical course of the disease is so variable, detection of the disease in affected patients has been difficult. When presence of the disease is confirmed in a community, however, prompt isolation of affected patients, good infection prevention and control practices, and rigorous contact tracing can stop outbreaks.

Key facts

• Lassa fever is an acute viral haemorrhagic illness of 2-21 days duration that occurs in West Africa.
• The Lassa virus is transmitted to humans via contact with food or household items contaminated with rodent urine or faeces.
• Person-to-person infections and laboratory transmission can also occur, particularly in hospitals lacking adequate infection prevention and control measures.
• Lassa fever is known to be endemic in Benin, Ghana, Guinea, Liberia, Mali, Sierra Leone, and Nigeria, but probably exists in other West African countries as well.
• The overall case-fatality rate is 1%. Observed case-fatality rate among patients hospitalized with severe cases of Lassa fever is 15%.
• Early supportive care with rehydration and symptomatic treatment improves survival.

Background

Though first described in the 1950s, the virus causing Lassa disease was not identified until 1969. The virus is a single-stranded RNA virus belonging to the virus family Arenaviridae.

About 80% of people who become infected with Lassa virus have no symptoms. 1 in 5 infections result in severe disease, where the virus affects several organs such as the liver, spleen and kidneys.

Lassa fever is known to be endemic in Benin (where it was diagnosed for the first time in November 2014), Ghana (diagnosed for the first time in October 2011), Guinea, Liberia, Mali (diagnosed for the first time in February 2009), Sierra Leone, and Nigeria, but probably exists in other West African countries as well.

Symptoms

The incubation period of Lassa fever ranges from 6–21 days. The onset of the disease, when it is symptomatic, is usually gradual, starting with fever, general weakness, and malaise. After a few days, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhoea, cough, and abdominal pain may follow. In severe cases facial swelling, fluid in the lung cavity, bleeding from the mouth, nose, vagina or gastrointestinal tract and low blood pressure may develop.

Protein may be noted in the urine. Shock, seizures, tremor, disorientation, and coma may be seen in the later stages. Deafness occurs in 25% of patients who survive the disease. In half of these cases, hearing...
returns partially after 1–3 months. Transient hair loss and gait disturbance may occur during recovery.

Death usually occurs within 14 days of onset in fatal cases. The disease is especially severe late in pregnancy, with maternal death and/or fetal loss occurring in more than 80% of cases during the third trimester.

Transmission

Humans usually become infected with Lassa virus from exposure to urine or faeces of infected *Mastomys* rats. Lassa virus may also be spread between humans through direct contact with the blood, urine, faeces, or other bodily secretions of a person infected with Lassa fever. There is no epidemiological evidence supporting airborne spread between humans. Person-to-person transmission occurs in both community and health-care settings, where the virus may be spread by contaminated medical equipment, such as re-used needles. Sexual transmission of Lassa virus has been reported.

Lassa fever occurs in all age groups and both sexes. Persons at greatest risk are those living in rural areas where *Mastomys* are usually found, especially in communities with poor sanitation or crowded living conditions. Health workers are at risk if caring for Lassa fever patients in the absence of proper barrier nursing and infection prevention and control practices.

Diagnosis

Because the symptoms of Lassa fever are so varied and non-specific, clinical diagnosis is often difficult, especially early in the course of the disease. Lassa fever is difficult to distinguish from other viral haemorrhagic fevers such as Ebola virus disease as well as other diseases that cause fever, including malaria, shigellosis, typhoid fever and yellow fever.

Definitive diagnosis requires testing that is available only in reference laboratories. Laboratory specimens may be hazardous and must be handled with extreme care. Lassa virus infections can only be diagnosed definitively in the laboratory using the following tests:

- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- antibody enzyme-linked immunosorbent assay (ELISA)
- antigen detection tests
- virus isolation by cell culture.

Treatment and prophylaxis

The antiviral drug ribavirin seems to be an effective treatment for Lassa fever if given early on in the course of clinical illness. There is no evidence to support the role of ribavirin as post-exposure prophylactic treatment for Lassa fever. There is currently no vaccine that protects against Lassa fever.

Prevention and control

Prevention of Lassa fever relies on promoting good “community hygiene” to discourage rodents from entering homes. Effective measures include storing grain and other foodstuffs in rodent-proof containers, disposing of garbage far from the home, maintaining clean households and keeping cats. Because *Mastomys* are so abundant in endemic areas, it is not possible to completely eliminate them from the environment. Family members should always be careful to avoid contact with blood and body fluids while caring for sick persons.

In health-care settings, staff should always apply standard infection prevention and control precautions when caring for patients, regardless of their presumed diagnosis. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe burial practices.

Health-care workers caring for patients with suspected or confirmed Lassa fever should apply extra infection control measures to prevent contact with the patient’s blood and body fluids and contaminated surfaces or materials such as clothing and bedding. When in close contact (within 1 metre) of patients with Lassa fever, health-care workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures).

Laboratory workers are also at risk. Samples taken from humans and animals for investigation of Lassa virus infection should be handled by trained staff and processed in suitably equipped laboratories under maximum biological containment conditions.

On rare occasions, travellers from areas where Lassa fever is endemic export the disease to other countries. Although malaria, typhoid fever, and many other tropical infections are much more common, the diagnosis of Lassa fever should be considered in febrile patients returning from West Africa, especially if they have had exposures in rural areas or hospitals in countries where Lassa fever is known to be endemic. Health-care workers seeing a patient suspected to have Lassa fever should immediately contact local and national experts for advice and to arrange for laboratory testing.

WHO response

The Ministries of Health of Guinea, Liberia and Sierra Leone, WHO, the Office of United States
Foreign Disaster Assistance, the United Nations, and other partners have worked together to establish the Mano River Union Lassa Fever Network. The programme supports these 3 countries in developing national prevention strategies and enhancing laboratory diagnostics for Lassa fever and other dangerous diseases. Training in laboratory diagnosis, clinical management, and environmental control is also included.

2. RIFT VALLEY FEVER

Overview
Rift Valley fever (RVF) is a viral zoonosis that primarily affects animals but also has the capacity to infect humans. Infection can cause severe disease in both animals and humans. The disease also results in significant economic losses due to death and abortion among RVF-infected livestock.

RVF virus is a member of the Phlebovirus genus. The virus was first identified in 1931 during an investigation into an epidemic among sheep on a farm in the Rift Valley of Kenya.

Since then, outbreaks have been reported in sub-Saharan Africa. In 1977 an explosive outbreak was reported in Egypt, the RVF virus was introduced to Egypt via infected livestock trade along the Nile irrigation system. In 1997–98, a major outbreak occurred in Kenya, Somalia and Tanzania following El Niño event and extensive flooding. Following infected livestock trade from the horn of Africa, RVF spread in September 2000 to Saudi Arabia and Yemen, marking the first reported occurrence of the disease outside the African continent and raising concerns that it could extend to other parts of Asia and Europe.

Key facts
• Rift Valley fever (RVF) is a viral zoonosis that primarily affects animals but can also infect humans.
• The majority of human infections result from contact with the blood or organs of infected animals.
• Human infections have also resulted from the bites of infected mosquitoes.
• To date, no human-to-human transmission of RVF virus has been documented.
• The incubation period (the interval from infection to onset of symptoms) for RVF varies from 2 to 6 days.
• Outbreaks of RVF in animals can be prevented by a sustained programme of animal vaccination.

Transmission in humans
The majority of human infections result from direct or indirect contact with the blood or organs of infected animals. The virus can be transmitted to humans through the handling of animal tissue during slaughtering or butchering, assisting with animal births, conducting veterinary procedures, or from the disposal of carcasses or fetuses. Certain occupational groups such as herders, farmers, slaughterhouse workers, and veterinarians are therefore at higher risk of infection.

The virus infects humans through inoculation, for example via a wound from an infected knife or through contact with broken skin, or through inhalation of aerosols produced during the slaughter of infected animals.

There is some evidence that humans may become infected with RVF by ingesting the unpasteurized or uncooked milk of infected animals.

• Human infections have also resulted from the bites of infected mosquitoes, most commonly the Aedes and Culex mosquitoes and the transmission of RVF virus by hematophagous (blood-feeding) flies is also possible.
• To date, no human-to-human transmission of RVF has been documented, and no transmission of RVF to health care workers has been reported when standard infection control precautions have been put in place.
• There has been no evidence of outbreaks of RVF in urban areas.

Clinical features in humans Mild form of RVF in humans
The following are clinical features of the mild form of RVF in humans:
• The incubation period (the interval from infection to onset of symptoms) for RVF varies from 2 to 6 days.
• Those infected either experience no detectable symptoms or develop a mild form of the disease characterized by a feverish syndrome with sudden onset of flu-like fever, muscle pain, joint pain and headache. Some patients develop neck stiffness, sensitivity to light, loss of appetite and vomiting; in these patients the disease, in its early stages, may be mistaken for meningitis.
• The symptoms of RVF usually last from 4 to 7 days, after which time the immune response becomes detectable with the appearance of antibodies and the virus disappears from the blood.
Severe form of RVF in humans

While most human cases are relatively mild, a small percentage of patients develop a much more severe form of the disease. This usually appears as 1 or more of 3 distinct syndromes: ocular (eye) disease (0.5–2% of patients), meningoencephalitis (less than 1% of patients) or haemorrhagic fever (less than 1% of patients).

The following are clinical features of the severe form of RVF in humans:

- **Ocular form:** In this form of the disease, the usual symptoms associated with the mild form of the disease are accompanied by retinal lesions. The onset of the lesions in the eyes is usually 1 to 3 weeks after appearance of the first symptoms. Patients usually report blurred or decreased vision. The disease may resolve itself with no lasting effects within 10 to 12 weeks. However, when the lesions occur in the macula, 50% of patients will experience a permanent loss of vision. Death in patients with only the ocular form of the disease is uncommon.

- **Meningoencephalitis form:** The onset of the meningoencephalitis form of the disease usually occurs 1 to 4 weeks after the first symptoms of RVF appear. Clinical features include intense headache, loss of memory, hallucinations, confusion, disorientation, vertigo, convulsions, lethargy and coma. Neurological complications can appear later (after more than 60 days). The death rate in patients who experience only this form of the disease is low, although residual neurological deficit, which may be severe, is common.

- **Haemorrhagic fever form:** The symptoms of this form of the disease appear 2–4 days after the onset of illness, and begin with evidence of severe liver impairment, such as jaundice. Subsequently signs of haemorrhage then appear such as vomiting blood, passing blood in the faeces, a purpuric rash or ecchymoses (caused by bleeding in the skin), bleeding from the nose or gums, menorrhagia and bleeding from venepuncture sites. The case-fatality ratio for patients developing the haemorrhagic form of the disease is high at approximately 50%. Death usually occurs 3 to 6 days after the onset of symptoms. The virus may be detectable in the blood for up to 10 days, in patients with the hemorrhagic icterus form of RVF.

The total case fatality rate has varied widely between different epidemics but, overall, has been less than 1% in those documented. Most fatalities occur in patients who develop the haemorrhagic icterus form.

**Diagnosis**

Because the symptoms of Rift Valley fever are varied and non-specific, clinical diagnosis is often difficult, especially early in the course of the disease. Rift Valley fever is difficult to distinguish from other viral haemorrhagic fevers as well as many other diseases that cause fever, including malaria, shigellosis, typhoid fever, and yellow fever.

Definitive diagnosis requires testing that is available only in reference laboratories. Laboratory specimens may be hazardous and must be handled with extreme care. Rift Valley fever virus infections can only be diagnosed definitively in the laboratory using the following tests:

- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- IgG and IgM antibody enzyme-linked immunosorbent assay (ELISA)
- virus isolation by cell culture.

**Treatment and vaccines**

As most human cases of RVF are relatively mild and of short duration, no specific treatment is required for these patients. For the more severe cases, the predominant treatment is general supportive therapy.

An inactivated vaccine has been developed for human use. However, this vaccine is not licensed and is not commercially available. It has been used experimentally to protect veterinary and laboratory personnel at high risk of exposure to RVF. Other candidate vaccines are under investigation.

**RVF virus in host animals**

RVF is able to infect many species of animals causing severe disease in domesticated animals including cattle, sheep, camels and goats. Sheep and goats appear to be more susceptible than cattle or camels.

Age has also been shown to be a significant factor in the animal’s susceptibility to the severe form of the disease: over 90% of lambs infected with RVF die, whereas mortality among adult sheep can be as low as 10%.

The rate of abortion among pregnant infected ewes is almost 100%. An outbreak of RVF in animals frequently manifests itself as a wave of unexplained abortions among livestock and may signal the start of an epidemic.

**Ecology and mosquito vectors**

Several different species of mosquito are able to act as vectors for transmission of the RVF virus. The dominant vector species varies between different regions and different species can play different roles in sustaining the transmission of the virus.

Among animals, the RVF virus is spread primarily by the bite of infected mosquitoes, mainly the *Aedes* species, which can acquire the virus from
feeding on infected animals. The female mosquito is also capable of transmitting the virus directly to her offspring via eggs leading to new generations of infected mosquitoes hatching from eggs.

However, when analysing RVF major outbreaks, 2 ecologically distinct situations should be considered. At primary foci areas, RVF virus persists through transmission between vectors and hosts and maintains through vertical transmission in Aedes mosquitoes. During major outbreak in primary foci, the disease can spread to secondary foci through livestock movement or passive mosquitoes dispersal and amplifies in naïve ruminants via local competent mosquitoes like Culex, Mansonia and Anopheles that act as mechanical vectors. Irrigation schemes, where populations of mosquitoes are abundant during long periods of the year, are highly favourable places for secondary disease transmission.

Prevention and control Controlling RVF in animals

Outbreaks of RVF in animals can be prevented by a sustained programme of animal vaccination. Both modified live attenuated virus and inactivated virus vaccines have been developed for veterinary use. Only 1 dose of the live vaccine is required to provide long-term immunity but this vaccine may result in spontaneous abortion if given to pregnant animals. The inactivated virus vaccine does not have this side effect, but multiple doses are required in order to provide protection which may prove problematic in endemic areas.

Animal immunization must be implemented prior to an outbreak if an epizootic is to be prevented. Once an outbreak has occurred animal vaccination should NOT be implemented because there is a high risk of intensifying the outbreak. During mass animal vaccination campaigns, animal health workers may, inadvertently, transmit the virus through the use of multi-dose vials and the re-use of needles and syringes. If some of the animals in the herd are already infected and viraemic (although not yet displaying obvious signs of illness), the virus will be transmitted among the herd, and the outbreak will be amplified.

Restricting or banning the movement of livestock may be effective in slowing the expansion of the virus from infected to uninfected areas.

As outbreaks of RVF in animals precede human cases, the establishment of an active animal health surveillance system to detect new cases is essential in providing early warning for veterinary and human public health authorities.

Public health education and risk reduction

During an outbreak of RVF, close contact with animals, particularly with their body fluids, either directly or via aerosols, has been identified as the most significant risk factor for RVF virus infection. Raising awareness of the risk factors of RVF infection as well as the protective measures individuals can take to prevent mosquito bites is the only way to reduce human infection and deaths.

Public health messages for risk reduction should focus on:

• reducing the risk of animal-to-human transmission as a result of unsafe animal husbandry and slaughtering practices. Practicing hand hygiene, wearing gloves and other appropriate individual protective equipment when handling sick animals or their tissues or when slaughtering animals.
• reducing the risk of animal-to-human transmission arising from the unsafe consumption of fresh blood, raw milk or animal tissue. In the epizootic regions, all animal products (blood, meat, and milk) should be thoroughly cooked before eating.
• the importance of personal and community protection against mosquito bites through the use of impregnated mosquito nets, personal insect repellent if available, light coloured clothing (long-sleeved shirts and trousers) and by avoiding outdoor activity at peak biting times of the vector species.
• Guide on safe food for travellers

Infection control in health care settings

Although no human-to-human transmission of RVF has been demonstrated, there is still a theoretical risk of transmission of the virus from infected patients to healthcare workers through contact with infected blood or tissues. Healthcare workers caring for patients with suspected or confirmed RVF should implement Standard Precautions when handling specimens from patients.

Standard Precautions define the work practices that are required to ensure a basic level of infection control. Standard Precautions are recommended in the care and treatment of all patients regardless of their perceived or confirmed infectious status. They cover the handling of blood (including dried blood), all other body fluids, secretions and excretions (excluding sweat), regardless of whether they contain visible blood, and contact with non-intact skin and mucous membranes.

• Standard precautions in health care

As noted above, laboratory workers are also at risk. Samples taken from suspected human and animal cases of RVF for diagnosis should be handled by trained staff and processed in suitably equipped laboratories.

Vector control

Other ways in which to control the spread of RVF involve control of the vector and protection against
their bites.
Larviciding measures at mosquito breeding sites are the most effective form of vector control if breeding sites can be clearly identified and are limited in size and extent. During periods of flooding, however, the number and extent of breeding sites is usually too high for larviciding measures to be feasible.

RVF forecasting and climatic models
Forecasting can predict climatic conditions that are frequently associated with an increased risk of outbreaks, and may improve disease control. In Africa, Saudi Arabia and Yemen RVF outbreaks are closely associated with periods of above-average rainfall. The response of vegetation to increased levels of rainfall can be easily measured and monitored by Remote Sensing Satellite Imagery. In addition RVF outbreaks in East Africa are closely associated with the heavy rainfall that occurs during the warm phase of the El Niño–Southern Oscillation (ENSO) phenomenon.
These findings have enabled the successful development of forecasting models and early warning systems for RVF using satellite images and weather/climate forecasting data. Early warning systems, such as these, could be used to trigger detection of animal cases at an early stage of an outbreak, enabling authorities to implement measures to avert impending epidemics.
Within the framework of the new International Health Regulations (2005), the forecasting and early detection of RVF outbreaks, together with a comprehensive assessment of the risk of diffusion to new areas, are essential to enabling the implementation of effective and timely control measures.

WHO response
For the 2016, Niger outbreak, WHO sent a multisectoral national rapid response team, including members from the Ministry of Health, veterinary services and Centre de Recherche Médicale et Sanitaire (CERMES). The unit was deployed for field investigation on 31 August 2016.
In Niger, the WHO Country Office provides technical and financial support for surveillance, outbreak investigation, technical guidelines regarding case definition, case management, shipment of samples, and risk communication.
The Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and WHO are coordinating on animal and human health and providing additional support to Niger for the outbreak response.
WHO is working with partners in the Global Outbreak Alert and Response Network (GOARN) to coordinate international support for the response.

The International Federation of Red Cross and Red Crescent Societies (IFRC) and UNICEF are supporting outbreak response.

3. ORAL HEALTH

Overview
Oral health is essential to general health and quality of life. It is a state of being free from mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit an individual’s capacity in biting, chewing, smiling, speaking, and psychosocial wellbeing.

Key facts
• Worldwide, 60–90% of school children and nearly 100% of adults have dental cavities.
• Dental cavities can be prevented by maintaining a constant low level of fluoride in the oral cavity.
• Severe periodontal (gum) disease, which may result in tooth loss, is found in 15–20% of middle-aged (35-44 years) adults.
• Globally, about 30% of people aged 65–74 have no natural teeth.
• Oral disease in children and adults is higher among poor and disadvantaged population groups.
• Risk factors for oral diseases include an unhealthy diet, tobacco use, harmful alcohol use and poor oral hygiene, and social determinants.

Oral diseases and conditions
The most common oral diseases are dental cavities, periodontal (gum) disease, oral cancer, oral infectious diseases, trauma from injuries, and hereditary lesions.
Dental cavities: Worldwide, 60–90% of school children and nearly 100% of adults have dental cavities, often leading to pain and discomfort.
Periodontal disease: Severe periodontal (gum) disease, which may result in tooth loss, is found in 15–20% of middle-aged (35-44 years) adults.
Tooth loss: Dental cavities and periodontal disease are major causes of tooth loss. Complete loss of natural teeth is widespread and particularly affects older people. Globally, about 30% of people aged 65–74 have no natural teeth.
Oral cancer: The incidence of oral cancer ranges from one to 10 cases per 100 000 people in most countries. The prevalence of oral cancer is relatively higher in men, in older people, and among people of low education and low income. Tobacco and alcohol are major causal factors.
Fungal, bacterial or viral infections in HIV: Almost half (40–50%) of people who are HIV-positive
have oral fungal, bacterial or viral infections. These often occur early in the course of HIV infection.

**Oro-dental trauma:** Across the world, 16-40% of children in the age range 6 to 12 years old are affected by dental trauma due to unsafe playgrounds, unsafe schools, road accidents, or violence.

**Noma:** Noma is a gangrenous lesion that affects young children living in extreme poverty primarily in Africa and Asia. Lesions are severe gingival disease followed by necrosis (premature death of cells in living tissue) of lips and chin. Many children affected by noma suffer from other infections such as measles and HIV. Without any treatment, about 90% of these children die.

**Cleft lip and palate:** Birth defects such as cleft lip and palate occur in about one per 500–700 of all births. This rate varies substantially across different ethnic groups and geographical areas.

**Common causes**

Risk factors for oral diseases include an unhealthy diet, tobacco use and harmful alcohol use. These are also risk factors for the four leading chronic diseases – cardiovascular diseases, cancer, chronic respiratory diseases and diabetes – and oral diseases are often linked to chronic disease. Poor oral hygiene is also a risk factor for oral disease.

The prevalence of oral disease varies by geographical region, and availability and accessibility of oral health services. Social determinants in oral health are also very strong. The prevalence of oral diseases is increasing in low- and middle-income countries, and in all countries, the oral disease burden is significantly higher among poor and disadvantaged population groups.

**Prevention and treatment**

The burden of oral diseases and other chronic diseases can be decreased simultaneously by addressing common risk factors. These include:

- decreasing sugar intake and maintaining a well-balanced nutritional intake to prevent tooth decay and premature tooth loss;
- consuming fruit and vegetables that can protect against oral cancer;
- stopping tobacco use and decreasing alcohol consumption to reduce the risk of oral cancers, periodontal disease and tooth loss;
- ensuring proper oral hygiene;
- using protective sports and motor vehicle equipment to reduce the risk of facial injuries; and
- safe physical environments.

Dental cavities can be prevented by maintaining a constant low level of fluoride in the oral cavity. Fluoride can be obtained from fluoridated drinking water, salt, milk and toothpaste, as well as from professionally-applied fluoride or mouth rinse. Long-term exposure to an optimal level of fluoride results in fewer dental cavities in both children and adults.

Most oral diseases and conditions require professional dental care, however, due to limited availability or inaccessibility, the use of oral health services is markedly low among older people, people living in rural areas, and people with low income and education. Oral health care coverage is low in low- and middle-income countries.

Traditional curative dental care is a significant economic burden for many high-income countries, where 5–10% of public health expenditure relates to oral health. In low- and middle-income countries, public oral health programmes are rare. The high cost of dental treatment can be avoided by effective prevention and health promotion measures.

**WHO response**

Public health solutions for oral diseases are most effective when they are integrated with those for other chronic diseases and with national public health programmes. The WHO Global Oral Health Programme aligns its work with the strategy of chronic disease prevention and health promotion. Emphasis is put on developing global policies in oral health promotion and oral disease prevention, including:

- building oral health policies towards effective control of risks to oral health;
- stimulating development and implementation of community-based projects for oral health promotion and prevention of oral diseases, with a focus on disadvantaged and poor population groups;
- encouraging national health authorities to implement effective fluoride programmes for the prevention of dental caries;
- advocacy for a common risk factor approach to simultaneously prevent oral and other chronic diseases; and
- providing technical support to countries to strengthen their oral health systems and integrate oral health into public health.

**4. AUTISM SPECTRUM DISORDERS**

**Overview**

ASD refers to a range of conditions characterised by some degree of impaired social behaviour, communication and language, and a narrow range of interests and activities that are both unique to the individual and carried out repetitively.
ASDs begin in childhood and tend to persist into adolescence and adulthood. In most cases the conditions are apparent during the first 5 years of life.

Individuals with ASD often present other co-occurring conditions, including epilepsy, depression, anxiety and attention deficit hyperactivity disorder (ADHD). The level of intellectual functioning in individuals with ASDs is extremely variable, extending from profound impairment to superior levels.

Key facts
- 1 in 160 children has an autism spectrum disorder (ASD).
- ASDs begin in childhood and tend to persist into adolescence and adulthood.
- While some people with ASD can live independently, others have severe disabilities and require life-long care and support.
- Evidence-based psychosocial interventions, such as behavioural treatment and parent skills training programmes, can reduce difficulties in communication and social behaviour, with a positive impact on wellbeing and quality of life for persons with ASD and their caregivers.
- Interventions for people with ASD need to be accompanied by broader actions for making physical, social and attitudinal environments more accessible, inclusive and supportive.
- Worldwide, people with ASD are often subject to stigma, discrimination and human rights violations. Globally, access to services and support for people with ASD is inadequate.

Epidemiology
It is estimated that worldwide 1 in 160 children has an ASD. This estimate represents an average figure, and reported prevalence varies substantially across studies. Some well-controlled studies have, however, reported figures that are substantially higher. The prevalence of ASD in many low- and middle-income countries is so far unknown.

Based on epidemiological studies conducted over the past 50 years, the prevalence of ASD appears to be increasing globally. There are many possible explanations for this apparent increase, including improved awareness, expansion of diagnostic criteria, better diagnostic tools and improved reporting.

Causes
Available scientific evidence suggests that there are probably many factors that make a child more likely to have an ASD, including environmental and genetic factors.

Available epidemiological data are conclusive that there is no evidence of a causal association between measles, mumps and rubella vaccine, and ASD. Previous studies suggesting a causal link were found to be filled with methodological flaws. (1), (2)

There is also no evidence to suggest that any other childhood vaccine may increase the risk of ASD. Evidence reviews of the potential association between thiomersal preservative and aluminium adjuvants contained in inactivated vaccines and the risk of ASD strongly concluded that vaccines do not increase the risk of ASDs.

Assessment and management
Intervention during early childhood is important to promote the optimal development and well-being of people with an ASD. Monitoring of child development as part of routine maternal and child health care is recommended.

It is important that, once identified, children with an ASD and their families are offered relevant information, services, referrals, and practical support according to their individual needs. A cure for ASD is not available. Evidence-based psychosocial interventions, however, such as behavioural treatment and skills training programmes for parents and other caregivers, can reduce difficulties in communication and social behaviour, with a positive impact on the person’s wellbeing and quality of life.

The health-care needs of people with ASD are complex and require a range of integrated services, including health promotion, care, rehabilitation services, and collaboration with other sectors such as the education, employment and social sectors.

Interventions for people with ASD and other developmental disorders need to be accompanied by broader actions for making their physical, social, and attitudinal environments more accessible, inclusive and supportive.

Social and economic impacts
ASDs may significantly limit the capacity of an individual to conduct daily activities and participate in society. ASD often negatively influence the person’s educational and social attainments as well as employment opportunities.

While some individuals with ASD are able to live independently, others have severe disabilities and require life-long care and support.

ASDs often impose significant emotional and economic burden on people with these disorders and their families. Caring for children with the severe spectrum of the condition may be demanding, especially where access to services and support are inadequate. Therefore the empowerment of caregivers is increasingly being recognized as a critical component of care interventions for children with ASD.
Human rights
People with ASD are often subject to stigma and discrimination, including unjust deprivation of health, education and opportunities to engage and participate in their communities.

People with ASD have the same health problems that affect the general population. Furthermore, they may have specific health care needs related to ASD or other co-occurring conditions. They may be more vulnerable to developing chronic noncommunicable conditions because of behavioural risk factors such as physical inactivity and poor dietary preferences, and are at greater risk of violence, injury and abuse.

People with ASD require accessible health services for general health-care needs like the rest of the population, including promotive and preventive services and treatment of acute and chronic illness. Nevertheless, people with ASD have higher rates of unmet health-care needs compared with the general population. They are also more vulnerable during humanitarian emergencies. A common barrier is created by health-care providers’ inadequate knowledge of ASD and misconceptions.

WHO Resolution on autism spectrum disorders (WHA67.8)
In May 2014, the Sixty-seventh World Health Assembly adopted a resolution entitled “Comprehensive and coordinated efforts for the management of autism spectrum disorders (ASD),” which was supported by more than 60 countries.

The resolution urges WHO to collaborate with Member States and partner agencies to strengthen national capacities to address ASD and other developmental disorders.

WHO response
WHO and its partners recognize the need to strengthen countries’ abilities to promote optimal health and well-being of all persons with ASD.

Efforts are focusing on:
• contributing to enhancing commitment of governments and international advocacy on autism;
• providing guidance on creating policies and action plans that address ASD within the broader framework of mental health and disabilities;
• contributing to the development of evidence on effective and scalable strategies for the assessment and treatment of ASD and other developmental disorders.

WHO, in consultation with experts, parents’ associations and civil society organizations developed a parent skills training programme which is currently undergoing field-testing.

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5. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Overview
Chronic obstructive pulmonary disease is a lung disease that is characterized by a persistent reduction of airflow. The symptoms of COPD are progressively worsening and persistent breathlessness on exertion, eventually leading to breathlessness at rest. It tends to be underdiagnosed and can be life-threatening. The more familiar terms “chronic bronchitis” and “emphysema” have often been used as labels for the condition.

Key facts
• Chronic obstructive pulmonary disease (COPD) is a progressive lifethreatening lung disease that causes breathlessness (initially with exertion) and predisposes to exacerbations and serious illness.
• Globally, it is estimated that about 3 million deaths were caused by the disease in 2015 (that is, 5% of all deaths globally in that year).
• More than 90% of COPD deaths occur in low and middle-income countries.
• The primary cause of COPD is exposure to tobacco smoke (either active smoking or second-hand smoke).
• Other risk factors include exposure to indoor and outdoor air pollution and occupational dusts and fumes.
• Some cases of COPD are due to long-term asthma.
• COPD is likely to increase in coming years due to higher smoking prevalence and aging populations in many countries.
• Many cases of COPD are preventable by avoidance or early cessation of smoking. Hence, it is important that countries adopt the WHO Framework Convention on Tobacco Control (WHO-FCTC) and implement the MPOWER package of measures so that non-smoking becomes the norm globally.
• COPD is not curable, but treatment can relieve symptoms, improve quality of life and reduce the risk of death.
Risk factors
The primary cause of COPD is tobacco smoke (including secondhand or passive exposure). Other risk factors may include:
- indoor air pollution (such as solid fuel used for cooking and heating)
- outdoor air pollution
- occupational dusts and chemicals (such as vapours, irritants, and fumes)
- frequent lower respiratory infections during childhood.

Many cases of COPD are preventable. Comprehensive implementation of the WHO FCTC will reduce smoking prevalence and the burden of COPD globally.

Who is at risk?
Previously COPD was more common in men, but because of comparably high levels of tobacco smoking among women in high income countries, and the higher risk of exposure to indoor air pollution (such as solid fuel used for cooking and heating) for women in low income countries, the disease now affects men and women almost equally.

More than 90% of COPD deaths occur in low and middle income countries, where effective strategies for prevention and control are not always implemented or accessible.

Symptoms
Chronic obstructive pulmonary disease develops slowly and usually becomes apparent after 40 or 50 years of age. The most common symptoms of COPD are breathlessness (or a “need for air”), chronic cough, and sputum (mucous) production. Daily activities, such as walking up a short flight of stairs or carrying a suitcase, and even daily routine activities can become very difficult as the condition gradually worsens. Sufferers also frequently experience exacerbations, that is, serious episodes of increased breathlessness, cough and sputum production that last from several days to a few weeks. These episodes can be seriously disabling and result in need for urgent medical care (including hospitalization) and sometimes death.

Diagnosis and treatment
Chronic obstructive pulmonary disease is usually suspected in people who experience the symptoms described above and can be confirmed by a breathing test called “spirometry” that measures how much and how quickly a person can forcibly exhale air.

Chronic obstructive pulmonary disease is not curable. However, available medical and physical treatments can help relieve symptoms, improve exercise capacity and quality of life and reduce the risk of death. The most effective and cost-effective available treatment for COPD in people who continue to smoke is smoking cessation. Smoking cessation can slow down the progress of the disease in smokers and decrease COPD-related deaths. In some, but not all, people with COPD, treatment with inhaled corticosteroid medicines has a beneficial effect.

The availability of diagnostic and treatment options for COPD differs across varying resource settings. WHO has released a guideline with specific recommendations for COPD management in primary health care in resource constrained settings.

WHO response
WHO’s work on COPD is part of the Organization’s overall efforts to prevent and control noncommunicable diseases. WHO aims to:
- raise awareness about the global epidemic of noncommunicable diseases;
- create more healthy environments, especially for poor and disadvantaged populations;
- decrease risk factors of noncommunicable disease, such as tobacco smoking and exposure to second-hand smoke, indoor and outdoor air pollution, unhealthy diet and physical inactivity;
- improve access to effective therapies for people with COPD; and
- prevent premature deaths and avoidable disabilities from major noncommunicable diseases.

The WHO Framework Convention on Tobacco Control was developed in response to the globalization of the tobacco epidemic to protect billions of people from harmful exposure to tobacco. It is the first global health treaty negotiated by WHO, and has been ratified by 180 countries.

WHO also leads the Global Alliance against Chronic Respiratory Diseases (GARD), a voluntary alliance of national and international organizations, institutions and agencies working towards the common goal of reducing the global burden of chronic respiratory diseases. Its vision is a world where all people breathe freely. GARD focuses specifically on the needs of low and middle-income countries and vulnerable populations.

REFERENCES