KUWAIT MEDICAL JOURNAL
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KMJ

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EDITORIAL

ORIGINAL ARTICLES

CASE REPORTS

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Continued inside

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C O N T E N T S

Continued from cover

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Burrows B, Lebowitz MD. The b agonists dilemma (editorial). N Engl J Med 1992; 326:560-561.

Book

Roberts NK. The cardiac conducting system and His bundle electrogram. New York, Appleton-Century-Crofts, 1981; 49-56.

Book chapter

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

Weblinks

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

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Editorial

What is Normal Blood Pressure?

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

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"When people cheat in any arena, they diminish themselves-they threaten their own self-esteem and their relationships with others by undermining the trust they have in their ability to succeed and in their ability to be true."

Cheryl Hughes

I have been wondering about this *normal blood pressure* for the last sixty years, ever since I joined the I MBBS class in 1956. In the physiology class I was wondering what this normal blood pressure was and how did they find out the normal level in the first place? My teacher was not able to answer that to my satisfaction, although she did not like my interference. Luckily in those days, the normal levels were much higher than now. I grew up in medicine and at some stage, became a member of the International Society of Hypertension, and met some of the "top" hypertensionologists to rub shoulders with them on an equal footing. None of them could quench my thirst. In the meantime, I was doing my own research (no money or grant involved) and have published some of them since then. I have also written a book on hypertension in 1996, published by the Bhavan in Mumbai with a foreword by one of the leading lights in the field, Barry Hoffbrand, the then editor of the British Postgraduate Medical Journal[1].

Here I stand O fool! With all my lore, no wiser than before about this enigma called normal blood pressure. Last month came another thunderbolt of a study (so called) proclaiming to the wide world that even "Normal" blood pressure needs to be treated with antihypertensive drugs to lower CVS and CNS mortalities and morbidities! On this side of the Atlantic, an ethnic Indian researcher was presenting a paper in the European Hypertension Society meeting, another study which shouts at the top voice that a deadly combination of hypertension and depression kills millions in this world, due to heart and brain attacks. He stressed that both must be vigorously hounded out of the human system to reduce heart and brain attacks! With this new study from Oxford of the need to treat even normal blood pressure, I realise that I have been searching for a non-existent *normal blood pressure* which does not matter after all!

This brings back to mind that famous saying of a great teacher of hypertension, Professor Sir George Pickering's tongue in cheek averment "More people in this world make a living "off" hypertension than dying "of" it. How very true? More curious am I about this drug treatment of depression along with hypertension to lower mortality. The human mind which gets depressed is not inside the human brain. Our reductionist chemical drugs that claim to treat depression, ONLY act on the brain, provoking suicidal tendencies and cannot obviously do anything for the unhappy mind. None of the anti-depressants have been shown to be better than a placebo! I was reading some of the original comments on the (in) famous Oxford study of the need to treat even normal BP. Some of them are here for the reader's benefit.

"Could our relentless pursuit of good health be making us sick? Advances in medicine have propelled health care to new heights and a vast array of diagnostic tests and drug therapies is now available. But are we getting too much of a good thing?", Australian TV comment.

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

"When I was a medical student, we used to define a normal blood pressure as being under 100 plus the person's age for the top number and 100 for the bottom number. Nowadays, it's 150/90, or if you're diabetic or you're worried about prehypertension, it's even as low as 140/80. By changing that threshold, you include millions more people in the range of abnormality and in the market for antihypertensive medication. This has raised questions about whether people with mild hypertension would benefit from blood-pressure medication, a Cochrane Review showed that most people with mild hypertension don't. The treatment of mild hypertension has had no benefit on either morbidity or mortality. That makes up the vast majority of people worldwide on treatment for hypertension." Ion Heath.

"I feel it's pretty arrogant to be so sure of the results of a partially completed study that it can be cut short!!!?? Finish the damn study!! This is why studies are NOT reliable, they are not finished, or info was manipulated or lost or some self-appointed untrained or money oriented person starts making treatments up. Usually there's some pharmaceutical company behind the studies….unless someone is saying to eat vegetables….and you can't patent that!"

"I smell a rat with this. The renormalisation of medical metrics has been going on since drug companies began trying to increase sales of medications. It's happened for cholesterol drugs, antidepressants and now blood pressure. What is normal, anyway? It seems we are less normal than we used to be - including the medical profession."

Coming back to our original study from Oxford which proclaimed that treating normal blood pressure with antihypertensive drugs is good to save millions of lives, I have several nagging questions. Incidentally, the study is published in the Lancet. It is retrospective meta-analysis of all studies done from 1953 till 2014. Obviously, this is what statisticians call the *Mix Master technique*. It is like putting all kinds of fruits in a basket and blindly putting your hand in to pick one fruit to be shown as the representative of all the fruits in the basket. This is otherwise called "doctoring or sexing up" studies to suit your conclusions to benefit your master, who has funded you. If the conclusions of this study are acted upon, drug companies will be richer by a thousand times.

Each one of the studies included in this meta-analysis has its own NNT (number needed to treat) and its own side effect profile. To give one example, the famous MRC study of mild to moderate hypertension published in the BMJ in 1985 has NNT of 850. That is to benefit one individual from stroke in the next five years one has to unnecessarily treat 850 healthy individuals with drugs which might have significant side effect in 75 individuals! Many such studies are included in this "great "study to make it in essence a company paid effort to get millions more to qualify to take antihypertensive drugs. What a way to "scientifically" increase one's profits? While the company executives might laugh all the way to their banks, many orphans and widows might be grieving in the cemetery! I smell a rat here.

Would anyone tell me what is normal BP anyway. I know the average human BP but not the NORMAL BP. If one converts averages into normals we are straight away adding between 5 - 25% false positives, another profitable business. RCTs, the multiple studies that form the basis of this conclusion, themselves, have been seriously questioned for their authenticity[2]. What is this circus all about? If blood is flowing laminarly inside the blood vessels, naturally it cannot exert any lateral pressure as Co Sine 90 is zero. So, what is Blood pressure?

"Recognition should come to the reporter who uncovers public cheating or proves a convicted man innocent."

Phil Donahue

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Original Article

Methylenetetrahydrofolate Reductase C677T Polymorphism in Sudanese Women with Recurrent Spontaneous Abortions

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ABSTRACT

Objective: To investigate the presence of Methylenetetrahydrofolate Reductase (MTHFR) C677T polymorphisms in pregnant women with a previous history of recurrent spontaneous abortions (RSA), and evaluate the impact on maternal and fetal outcomes
Design: A prospective analytical case control study
Setting: Omdurman Maternity Hospital, Sudan
Subjects: One hundred Sudanese women who experienced three or more of the adverse pregnancy outcomes during their reproductive age (case group) and 94 healthy women (control group) of at least more than two normal pregnancies and without any history of adverse pregnancy outcome or recurrent miscarriages were included in this study.
Interventions: The study group data collected using structure questionnaire to collect information and DNA was extracted from peripheral bloods and analyzed for the presence of Methylenetetrahydrofolate Reductase C677T polymorphisms. Data were entered and analyzed by SPSS programme (version: 17.0) and compared with other international studies.
Methods: This prospective analytical case control study was carried out at Omdurman Maternal Hospital, Sudan between July 2012 to Nov. 2014. The study included one hundred pregnant women with a history of recurrent spontaneous abortion (as case group) and ninety-five healthy reproductive Sudanese women (as control group). Identification of MTHFR C677T polymorphism, by polymerase chain reaction was performed.
Main outcome measures: The relationship between the MTHFR C677T polymorphisms and recurrent spontaneous abortion was investigated.
Result: The frequency of Heterozygous C/T MTHFR gene was 3.0% in cases with p-value 0.091 and there was no mutant allele detected among the control group.
Conclusion: Our study results showed no significant variations in MTHFR C677T genotype distribution among women who suffered from RSA and controls. Further studies on larger population may be needed.

KEYWORDS: MTHFR C677T, polymorphisms, pregnancy loss, spontaneous miscarriage, sudanese pregnant women

INTRODUCTION

Recurrent miscarriage (RM), which is also referred to as repeated pregnancy loss (RPL) and habitual abortion, is defined as three or more consecutive spontaneous miscarriages. The experience of repeated pregnancy loss is physically and emotionally traumatic to women who are trying to have children. The overall frequency of RM was estimated from 1 - 3 %[1] . Recurrent pregnancy loss is classically defined as three or more consecutive losses. There is some debate, however, about the definition of recurrent pregnancy loss. Some feel that two rather than three losses are sufficient to define recurrent pregnancy loss; some include only first-trimester miscarriages, whereas others include second-trimester losses[2]. Molecular studies of coagulation disorders have led to the discovery of an increasing number of mutations in the genes of the factors of coagulation, termed

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inherited thrombophilia (IT). Most important of this group are factor V gene Leiden mutation G1691A (FVL), prothrombin G20210 (FII), homozygosity for the thermo labile of methyltetrahydrofolate reductase deficiency C677T (MTHFR), antithrombin deficiency, protein C deficiency, and protein S deficiency[3,4]. Various reports have postulated thrombophilia as a risk for recurrent spontaneous abortions (RSA). Deficiency in the homocysteine metabolism pathway resulting in an elevation of homocysteine level in plasma (hyperhomocystinemia) has been regarded as a cause of Thrombophilia[5]. Methylenetetrahydrofolate reductase (MTHFR) is one of the main regulatory enzymes in the metabolism of homocysteine that catalyses the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate[6]. Mutations in MTHFR gene lead to decreased activity of enzyme and hyperhomocystinemia, which induces platelet aggregation through promotion of endothelial oxidative damage. Although there are several mutations within the MTHFR gene, but C677T and A1298C mutations are the two most common mutations[7], C677T transition is a missense mutation in the exons four of this gene, which converts an alanine to a valine codon (at codon 222) in the N-terminal catalytic domain of the protein leading to a thermo labile protein, with decreased enzymatic activity[8]. Also, the C677T MTHFR polymorphism is responsible for a decreased MTHFR activity and associated with increased plasma homocysteine concentrations that are induced for a folate metabolism disturbance[9]. The second mutation is MTHFR A1298C, which is associated with decreased activity of enzyme, but not with thermo ability. A1298C transversion is a point mutation in exon7, characterized by a glutamate to alanine substitution (at codon 429) within the C-terminal regulatory domain of the protein[10].

Some previous study results conducted to show association of these factors and RPL reported that the different prevalence of these mutations and polymorphism in different populations depending on ethnic back ground could explain these differences[11,12].

SUBJECTS AND METHOD

After consents were obtained from the patients, the genomic DNA samples of 194 Sudanese women who were recruited and followed-up at Omdurman Maternal hospital were screened from July 2012 to Nov. 2014. One hundred females having a history of RPL as case were compared to 96 healthy reproductive Sudanese women as control group. Cases and controls were tested for the MTHFR C677T Polymorphism. DNA was isolated by the standard method, from 3 ml EDTA-blood samples[13]. DNA was extracted from the blood samples using Master pure DNA purification kit for blood GF-1 Blood DNA Extraction Kit, 50 PREPS (cat. No. GF-BD-050, Vivantis Technologies Sdn. Bhd., Malaysia). MTHFR C677T alleles and genotypes were determined by PCR using specific primers Forward (5′ TGA AGG AGA AGG TGT CTG CGG GA-3′) and Reverse primers: 5′AGG ACG GTG CGG TGA GAG AGT G -3′.A and their reaction program was as follows: Denaturation at 94 °C for 30 seconds, annealing at 51 °C for 30 seconds, extension at 72 °C for 30 seconds for 35 cycles and 72 °C for five minutes[14].

A master mix was prepared by adding Nuclease free water,10x buffer, dNTP, tow primers, $Mgcl_2$, Taq DNA polymerase and DNA, the mixture was loaded into thermocycler according to the specific Temperature profile. The working solution of 1 x TBE is prepared from the stock solution (1 L) which contains the following: 89 mM Tris base (108 gm), 89 mM boric acid (55 gm) 40 ml of 0.5M EDTA, adjust pH to 8.0.1.5% agarose was prepared from 1 x TBE, and 5 µl PCR products was loaded by mixing PCR products with 1 µl loading dye, run on the gel for 30 mins and visualized on UV transllimantor. Added the master mix reagents into the 0.5 ml PCR tube started with water, and the enzyme at the latest stage, mixed well by pipptting up and dawn, preferably quick spin for seconds to collect the reagents to the bottom, to insure complete digestion and proper environment for setting the mixture working all the time on ice , by adding 10 µl mixtures to the 10 µl MTHFR products, a quick spinning is needed, 5-incubated at 37 ºC for 18 hours, and the reaction was stopped with 4 µl prom phenol blue dye, and then, 18 µl digested products was loaded into 2% agarose[15].

The wild-type DNA yields a solitary gave (198 bp) band and heterozygous mutation yields three bands (198, 175, 23 bp) respectively, and homozygous mutation yields two bands of (175, 23 bp)[16]

Data analysis

Data were entered and analyzed by SPSS prograrmme (version: 17.0). All demographic data of the study population were presented as mean ± SD in the text and Odds Ratio (OR) was used for detecting the power of relationship between the determinant and the outcome, and 95% confidence interval (CI) was calculated. Data were analyzed using the Chi-square test for comparison the prevalence of MTHFR mutation between patients and controls (The test considered significant when p-value <0.05).

Ethics

Consent was obtained from the ethical committee of the Faculty Research Board and Hospital of Omdurman Maternity Hospital (Sudan).

RESULTS

Analyzing MTHFR gene mutations among RSA and controls were done using PCR-RFLP method. The Specific amplification of a 198-bp DNA fragment of the MTHFR gene surrounding nucleotide 677 products was digested overnight with Hinf1 on 2% agarose gel and the digestion products were separated by polyacrylamide gel electrophoresis. Staining with ethidium bromide and UV visualization resulted in the identification of the different genotypes.

The frequency of Heterozygous C/T MTHFR gene was 3.0% in cases with p-value = 0.091, there was no mutant gene were detected among the controls group. Normal homozygous gene was 97.0% in cases and 100% show in controls. The frequency of Alleles C was 98.5% in cases and 100% in controls while Alleles T was 1.5% in cases and not detected in controls. (Table 1). There was no significant association between cases carriage any of this mutation and risk of recurrent miscarriage. Example of the PCR results are presented in Fig 1.

Table 1: Genotype and allele frequencies of C677T polymorphisms of MTHFR in case and controls:

Genotype	Patients n (%)	Controls n (%)	P-value	OR (95% CI)
Heterozygous C/T	3 (3.0)	0	0.091	0
Normal homozygous C/C	97 (97.0)	94 (100)		
Alleles T	3 (1.5)	0	0.089	0
Alleles C	194 (98.5)	188 (100)		

OR = odds ratio, CI = confidence interval

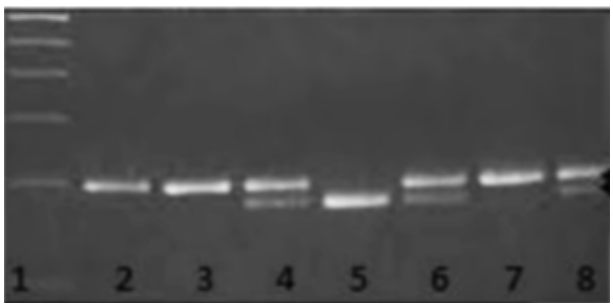

Fig 1: Detection of MTHFR polymorphisms on 2% agarose gel. Lane 1 molecular weight marker 100 bp, lane 2 undigested (198 bp), lane 3 and 6 were wild type (CC), Lane 4,6 and 8 were heterozygous mutant (CT), lane 5 was Control homozygous mutant (TT)

DISCUSSION

The prevalence of MTHFR C677T variant among women with recurrent miscarriage is still a matter of controversy. In our study, we found that they did not find the results significant between this gene and recurrent pregnancy loss among those women, and the frequency of Heterozygous C/T MTHFR gene was 3.0% in cases with P- Value 0.091 and there was no mutant gene detected among the controls group. Our finding is in agreement with several other studies that found no statistically significant difference between MTHFR C677T and recurrent pregnancy loss. One of these studies by Hasan and Sara[17], among Iraqi women with recurrent abortion, reported that there was no significant difference in the prevalence of 677T/T genotype among women with RSA and healthy controls (p = 0.37). Also, no statistically significant difference in the frequency of A1298C MTHFR gene mutation was detected between the two groups (P = 0.23). In a similar study done by Ahmed *et al* [18] in women with recurrent spontaneous abortions in the Northwest of Iran, the frequencies of MTHFR 677T and MTHFR 1298C alleles were (23.4%, 34.8%) in patients and (24%, 40%) and concluded with no significant variations in MTHFR C677T and A1298C genotype distribution among patients who suffered from RSA and controls. Also, this result was in agreement with earlier investigations reported by Goodman *et al*,[19] and Yenicesu *et al*[20] which reported no association between MTHFR and RSA. Our study is also in agreement with another study by Abu-Asab, *et al*[21] among Palestinian women with recurrent spontaneous abortion. Our analysis had failed to find a significant association between MTHFR and RPL in either the first or second trimester.

Our finding disagreed with findings from several other large studies that determine a significant association between the MTHFR C677T mutation and the presence of recurrent miscarriage during pregnancy. Behjati *et al*[22] and Jeddi *et al*[23] also found that there is a significant association between this gene mutation and recurrent pregnancy loss. Our study also disagrees with the findings of another study done by Mtiraoui *et al*[24] among 200 Tunisian women with more than three consecutive RPLs and 200 age-matched parous control women. They found that the frequency of MTHFR 677T/T (30.0 vs 7.0%) and 1298C/C (13.5 vs 4.0%) genotypes was significantly higher in patients and concluded that homozygosity for MTHFR C677T were the risk factors for RPL.

It is noteworthy that not all retrospective studies showed a relationship between the MTHFR C677T gene mutation and obstetric complications. Several case control studies failed to show any association between this mutation and abruption. Explanations for differences in results among studies may include different ethnic populations, different definitions for adverse outcomes, combining thrombophilias or adverse outcomes or both into summary statistics, and /or incomplete data regarding the gestational age of lost pregnancies. In addition, the difference in sample size between various studies may also be a good determinant in obtaining opposite conclusions.

CONCLUSION

In our study, we found that mutation of MTHFR C677T didn't increase risk for spontaneous recurrent abortion and had low frequency in the population studied. The possible explanations for the diversity of results among the literature reports related to MTHFR C677T mutation could be, the ethnic difference of the studied groups or the sample size used, which may justify the absence of association. Other genetic and environmental risk factors could also have contributed to the development of spontaneous recurrent abortion in the population we studied.

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Original Article

Reliability of the Infrared and Chemical Dot Temperature Measurement Methods in the Children Admitted in the Pediatric Emergency Unit: A Prospective Study

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ABSTRACT

Objectives: To determine the most comfortable measurement closest to rectal measurement of body temperature, which is the gold standard in measurement of core temperature
Design: Prospective study
Setting: Ondokuz Mayıs University Medical Faculty, Department of Pediatrics, Samsun, Turkey
Subjects: Temperature measurement was performed by four different methods during same fever period in 354 patients brought to our pediatric emergency unit (PEU) due to complaint of fever.
Interventions: This study aimed to determine the best alternative method, compared with rectal measurement, for detecting fever in pediatric patients aged between three months and three years, in whom fever may be the unique finding of an existing serious bacterial infection.
Main outcome measures: In each patient; temperature measurement was performed by rectal (RT), axillary (AT), temporal artery (TAT) and tympanic membrane (TMT) methods using digital, chemical dot, and infrared thermometer, respectively.
Results: There were 222 male and 132 female patients with a mean age of 19.45 ± 13.99 months. The area under the curve (AUC) values of AT, TAT and TMT measurements were 0.950, 0.861 and 0.917 ($p < 0.001$, $p < 0.001$ and $p < 0.001$), respectively. Inter Class Correlation (ICC) values of AT, TAT and TMT measurements in the febrile patients compared with rectal temperature were 0.86, 0.67 and 0.79, respectively. AT measurement method had the highest detected sensitivity compared with rectal temperature (85.71).
Conclusion: AT measurement method was the most reliable and comfortable measurement method among non-invasive measurement techniques in emergency service applications compared with RT.

KEYWORDS: discomfort, emergency, febrile, thermometer, temperature

INTRODUCTION

Patients, whose only complaint is fever, make up 10.5 - 25% of emergency service cases in childhood. The most common reason to apply emergency services to children aged <3 years is fever[1]. Viral infections are the most common cause of fever in patients aged between three months and three years, although the incidence of serious bacterial infection (SBI) ranges between 5 - 7% in this age group. Serious bacterial infections occurring with fever as the initial finding include pneumonia, meningitis, urinary tract infection, septic arthritis and osteomyelitis[2-3]. Emergency service physicians usually consider that SBI is based on level of body temperature and order advanced investigations to make their diagnostic and therapeutic decisions[4]. A false-negative measurement of body temperature may delay diagnosis and treatment of a serious disease, while a false-positive measurement may lead to unnecessary diagnostic tests[5]. Therefore, the methods of temperature measurement used in pediatric emergency units (PEU) for detecting a serious bacterial infection that presented with fever should be efficient, fast, accurate, safe and comfortable.

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Invasive and non-invasive measurement methods are used in detecting body temperature. The most important reasons for preferring temperature measurement methods are easy applicability and reliability. The best invasive method of detecting core temperature is temperature measurement of the pulmonary artery. However, this measurement method cannot be applied outside of intensive care units[5]. Therefore, rectal temperature measurement that shows the child's central core temperature, a less invasive method, is accepted as the gold standard[6]. Although rectal temperature measurement is commonly used in many healthcare institutions worldwide[4], it has important disadvantages, such as perforation, emotional stress and transmission of microorganisms possibly including HIV[4,7]. This situation motivated physicians, especially in emergency services, to apply alternative methods and measurement references in determining the body temperature[4,6-8]. The most widely used of these alternative methods are measurements using infrared, digital and chemical dot thermometers[4, 6-7, 9].

This study aimed to determine the best alternative method, compared with rectal measurement, for detecting fever in pediatric patients aged between three months and three years in whom, fever may be the unique finding of an existing serious bacterial infection.

MATERIAL AND METHODS

Study design and patient selection

This prospective comparative study was conducted in a tertiary medical center with 30,000 patient visits to the PEU annually. The study population included 354 pediatric patients, both febrile and afebrile, aged between three and 36 months between January to June 2014. All patients were randomly selected. Ethical approval for this prospective study was obtained from the Local Ethics Committee of Ondokuz Mayis University, in accordance with the Helsinki Declaration. Informed consent for participation was obtained from all parents.

Patients were excluded from the study, if their condition precluded inaccurate temperature measurement and no response to physical stimuli for consistency of Discomfort Scale Score (DSS). These patients who are too ill, uncooperative, crying, unconscious and with malignant hyperthermia, serious anemia, severe dehydration, protein energy malnutrition, presence of abnormal rectal and ear anatomy, serious wasting according to the WHO classification and those with major congenital anomalies were excluded.

Temperature measurements

The PEU ambient temperature during the study period was between 24 ºC and 28 ºC. All temperature measurements were taken by the same trained nurse and were performed according to the manufacturer's guidelines. Temperature was measured by four different methods during the same fever period in the 354 patients with complaint of fever. All measurements were performed with an interval of 15 s. The first measurement was made with temporal infrared thermometer (PlusMed® model pM 1-802). The second measurement was made with infrared tympanic thermometer (Genius™ 2 Infrared Tympanic Thermometer). The third measurement was made with axillary chemical dot thermometer (NexTemp single use thermometer, made in USA). The last measurement was made with rectal digital thermometer (BV130MR Digital Rectal Thermometer). The presence of fever was accepted by Rectal temperature (RT) ≥38 ºC[10-11].

Discomfort assessment

To assess patient discomfort due to different thermometers, Discomfort Scale Score (DSS) used by Greenes *et al*[12] was conducted (Table 1). Discomfort scores were assigned by trained nurses after they had taken temporal artery, tympanic membrane, axillary, and rectal temperature measurements.

Table 1: Discomfort Scale Score for Infants*

Clinical Sign	Description of Sign
Drowsy/asleep	Eye closed, may respond to stimulation
Relaxed	Sitting or lying with eyes open,
Anxious	Verbally or nonverbally seeks support
Upset	Tearful, may be clinging to parent
Agitated	General loud or high-pitched crying, requires significant physical restraint

*Adapted from Greenes *et al*

Sample size

Power analysis was performed to determine the study population. At least 45 patients were required to achieve a study power of 99% with α error = 0.05[7]

Statistical analysis

All data were analyzed using IBM SPSS 21.0 Software (Chicago, USA). Body temperature measurement values were expressed as mean ± standard deviation, while DSSs were given as median and minimum-maximum values. Group comparisons were performed by non-parametric methods: the Kruskall-Wallis and Mann-Whitney U tests. Rectal body temperature was accepted as the reference value; a reading of ≥38 ºC was accepted to indicate the presence of fever. AUC and cut-off values were determined for the other measurement methods using Receiver

Table 2: The values of AUC and cut off point of AT, TAT, and TMT methods according to ROC analysis

	Cut-off value	AUC	95% CI	p-value
AT	37.45 ºC	0.950	0.928 - 0.971	<0.001
TAT	37.15 ºC	0.861	0.822 - 0.899	<0.001
TMT	37.25 ºC	0.917	0.888 - 0.946	<0.001

AT = Axillary temperature, TAT = Temporal artery temperature, TMT = Tympanic membrane temperature, AUC = Area under the curve, CI = Confidence interval

Operating Characteristic (ROC) analysis. Interclass correlation coefficients were calculated with Package ICC of R project Programme. Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and likelihood ratios were calculated according to the RT accepted as the reference value. The correlation between variables was calculated using Spearman's correlation analysis. Correlation between the reference RT and other measurement methods was determined by linear regression analysis. Statistical significance was accepted as $p < 0.05$.

analysis were represented in Table 2. The numbers of the patients accepted as febrile and afebrile according to the measurement methods, and their mean body temperatures resulting from these calculated values, were represented in Table 3.

We analyzed the interclass correlation coefficients among temperatures measured by RT and by AT, TAT and TMT (Table 4). Correlations were assessed in all measurements. In the febrile and afebrile patients, a statistically significant positive correlation among all measurement methods compared with RT was present (Table 4). Among the febrile and afebrile patients, the closest correlation with RT was found in AT (ICC: 0.86 and 0.78, respectively). The 95% limits of agreements between AT and RT in febrile and afebrile groups were 0.81 to 0.89 and 0.70 to 0.84, respectively. In the febrile and afebrile patients, the weakest correlation with RT was found by TAT (ICC: 0.67 and 0.67, respectively). The 95% limits of agreements between TMT and RT in febrile and afebrile groups were 0.72 to 0.84 and 0.64 to 0.81, respectively (Table 4).

Table 3: Number of febrile and afebrile patients and temperatures according to different methods

	n	RT (mean ± SD)	n	AT (mean ± SD)	n	TAT (mean ± SD)	n	TMT (mean ± SD)
Febrile	196	38.77 ± 0.62	186	38.18 ± 0.50	191	37.79 ± 0.46	185	37.97 ± 0.52
Afebrile	158	37.33 ± 0.41	168	36.77 ± 0.39	163	36.65 ± 0.36	169	36.62 ± 0.40
Total	354		354		354		354	

AT = Axillary temperature, RT = Rectal temperature, TAT = Temporal artery temperature, TMT = Tympanic membrane temperature

RESULTS

This study included 354 patients, 222 (62.7%) female and 132 (37.3%) male. Their mean age was 19.45 ± 13.99 months. Body temperature values measured by rectal, temporal, axillary and tympanic methods in each patient were recorded. The cases were grouped as febrile and afebrile according to the rectal temperature value measured at initial admission. No hypothermic patient was detected in the study. AUC and cut-off values of axillary temperature (AT), temporal artery temperature (TAT), and tympanic membrane temperature (TMT) according to ROC

The rates of sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios of temporal, axillary and tympanic thermometers in detecting fever according to RT (≥38 ºC) were represented in Table 5. According to these values, the measurement method with the highest sensitivity was AT performed by chemical dot thermometer. The positive predictive value of the AT method was 90.32 (95% CI 85.14-94.16), while its negative predictive value was 83.33 (95% CI 76.82-88.63).

Table 4: Comparison of all measurement methods between in febrile and afebrile groups

Groups	ICC	p-value	Regression equation	Limits of agreement (95% CI)
Febrile patients				
AT vs RT	0.86	<0.001	RT = 10.101 + 0.753*AT	0.81 - 0.89
TAT vs RT	0.67	<0.001	RT = 20.493 + 0.486*TAT	0.57 - 0.75
TMT vs RT	0.79	<0.001	RT = 15.201 + 0.623*TMT	0.72 - 0.84
Afebrile patients				
AT vs RT	0.78	<0.001	RT = 15.529 + 0.592*AT	0.70 - 0.84
TAT vs RT	0.67	<0.001	RT = 20.518 + 0.457*TAT	0.56 - 0.76
TMT vs RT	0.74	<0.001	RT = 19.659 + 0.482*TMT	0.64 - 0.81

ICC; Interclass Correlation Coefficient, CI; Confidence Interval, AT; Axillary Temperature, RT; Rectal Temperature, TAT; Temporal Artery Temperature, TMT; Tympanic Membrane Temperature.

Table 5: The reliability rates of all temperature methods according to RT

AT		TAT		TMT	
Sensitivity (%)	**95% CI**	**Sensitivity (%)**	**95% CI**	**Sensitivity (%)**	**95% CI**
85.71	80.02 - 90.29	79.08	72.71 - 84.55	83.16	77.17 - 88.12
Specificity (%)					
88.61	82.59 - 93.10	77.22	69.88 - 83.50	86.08	79.68 - 91.06
PPV					
90.32	85.14 - 94.16	81.15	74.87 - 86.43	88.11	82.55 - 92.39
NPV					
83.33	76.82 - 88.63	74.85	67.46 - 81.30	80.47	73.68 - 86.16
LR (+)					
7.52		5.97		3.47	
LR (-)					
0.16		0.19		0.27	

AT; Axillary temperature, TAT; Temporal artery temperature, TMT; Tympanic membrane temperature, PPV; Positive predictive value, NPV; Negative predictive value, CI; Confidence interval, LR; Likelihood ratio.

When discomfort scores of the febrile and afebrile groups were compared according to all measurement methods, a statistically significant difference was found ($p < 0.001$ and $p < 0.001$, respectively) (Table 6). When discomfort scores of all measurement methods were compared, discomfort scores due to RT measurement were statistically significantly higher than those, due to other methods in both febrile and afebrile groups (Table 6). When groups were compared according to pairs of TAT, AT and TMT, no significant difference was found with respect to discomfort scores in both febrile (TAT vs TMT: $p = 0.925$, TAT vs AT: $p = 0.298$, TMT vs AT: $p = 0.331$) and afebrile (TAT vs TMT: $p = 0.323$, TAT vs AT: $p = 0.0.037$, TMT vs AT: $p = 0.252$) groups. In all measurement groups, a significant difference was found between discomfort scores of the febrile patients and those of the afebrile patients using the same measurement method (Table 6). When effects of the measurement methods on DSS were analyzed, only AT measurement had no effect on DSS ($r = 0.093$, $p = 0.081$). In contrast, RT, TAT and TMT were effective on DSS ($r = 0.251$, $p<0.001$, $r = 0.213$, $p <0.001$, and $r = 0.175$, $p = 0.001$, respectively).

Table 6: Comparison of DSS of all temperature measurement methods

Groups	RT	AT	TAT	TMT	p**
Febrile patients	4 (1-5)	3 (1-5)[a]	3 (1-5)[a]	3 (1-5)[a]	<0.001
Afebrile patients	4 (1-5)	2 (1-5)[b]	2 (1-5)[b]	2 (1-5)[b]	<0.001
p*	<0.001	0.007	<0.001	0.003	

DSS; Discomfort scale score, AT; Axillary temperature, RT; Rectal temperature, TAT; Temporal artery temperature, TMT; Tympanic membrane temperature.

[a], p <0.001 compared to RT groups in febrile patients (*Mann Whitney-U test).

[b], p <0.001 compared to RT groups in afebrile patients (*Mann Whitney-U test).

(** Kruskall Wallis Test)

DISCUSSION

This study analyzed 354 patients, 195 febrile and 159 afebrile, to determine the most reliable and comfortable alternative measurement method to rectal temperature, the gold standard in pediatric patients temperature checking (between three months and three years old), who were brought to the Pediatric emergency service with a complaint of fever. Infrared, digital and chemical dot temperatures were used as temperature measurement methods. According to obtained data, axillary temperature measurement using a chemical dot thermometer showed the best correlation with digital rectal temperature measurement. Alternative methods were found to be more comfortable than rectal temperature measurement.

Temperature measurement sites include regions such as the rectum, the tympanic membrane, the pulmonary artery, oral and sublingual sites, the esophagus, the temporal artery and the forehead skin[5,7,13]. These methods are classified as invasive and non-invasive based on application methodology. Use of a non-invasive and reliable method that reflects core temperature most accurately is preferable for emergency service staff[14]. Invasive methods that reflect core temperature to the highest accuracy include temperature measurements using a thermistor probe from the pulmonary artery, distal esophagus or tympanic membrane[15]. Among these invasive methods, pulmonary artery temperature is accepted as the gold standard in measurement of core temperature[5]. However, invasive methods such as temperature measurement in the pulmonary artery are generally used only in monitored patients under anesthesia in the intensive care unit[5]. Studies have shown that rectal temperature measurement produces results closest to the pulmonary artery temperature[16-17]. Therefore, rectal temperature

measurement is still accepted as the gold standard in evaluating the presence of fever in children[5-6]. However, some complications of rectal temperature measurement[4,7] have prompted physicians to use alternative noninvasive methods *via* infrared, chemical dot and digital technologies[18].

Different results have been reported in the literature on efficacy and applicability of the alternative temperature measurement methods on febrile patientss[4,6,9,18-20]. El Radhi and Patel compared body temperature measurements from the tympanic, axillary and rectal regions using infrared and digital thermometers in their study conducted on 106 infants. They stated in this study that the infrared tympanic membrane thermometer was more reliable than the digital axillary thermometer, and that it may be used in emergency units[10]. Paes *et al*[4] compared RT with infrared tympanic membrane and infrared skin thermometers in their study on 100 patients aged 0 - 18 years. They reported that infrared measurement methods were not as reliable as RT and that infrared tympanic membrane measurement may be preferred to an infrared skin thermometer when rectal measurement is not used. This study found the sensitivity and specificity of tympanic membrane thermometers to be 80% and 97% respectively, while those of infrared skin thermometers were found to be 64% and 96% respectively[4]. Muma *et al*[18] emphasized in another study that infrared tympanic membrane measurement has quite a low sensitivity (55%) in pediatric patients below three years old and that sensitivity of axillary measurement with electronic thermistor probes was found to be similar (48%). Besides these conflicting publications on tympanic membrane and skin measurements with infrared thermometers, medical literature on measurements obtained from the temporal artery is very limited. Siberry *et al* [21] found in their study that the sensitivity of temperature measurement from the temporal artery is 66% and that it is negatively predictive in measurement of body temperature. Brennan *et al*[19] also emphasized in their study on children aged between six months and six years that temporal artery measurement has weaker sensitivity than rectal measurement. Differently from these studies, Titus *et al*[20] reported that a temporal artery thermometer is an effective measurement method in screening fever in children aged 1 - 4 years. Allegaert *et al*[6] compared rectal measurement with measurements performed by infrared tympanic membrane, skin and temporal artery thermometers in their study on 294 children aged 0 - 17 years. They reported that all noninvasive infrared techniques have insufficient reliability compared to rectal measurement; however, temporal artery measurement is the closest technique to rectal measurement, although it is not an ideal method[6]. This study calculated sensitivity and specificity values of the infrared tympanic membrane thermometer, infrared skin thermometer and temporal artery thermometer as 22% and 100%, 27% and 100%, and 41% and 98%, respectively. A study that compared pulmonary artery, temporal artery, rectal and axillary measurement methods in 44 monitored patients in a Pediatric intensive care unit reported that rectal temperature is as reliable as pulmonary artery temperature. The same study stated that noninvasive measurement methods such as temporal artery and axillary measurement are not as accurate as rectal temperature measurements. It also stated that it would be appropriate to prefer noninvasive temporal artery measurement to axillary measurement in circumstances where invasive methods cannot be performed. The study reported sensitivity and specificity rates of the axillary thermometer as 60% and 100% respectively, whereas sensitivity and specificity rates of the temporal artery thermometer were found to be 44% and 89% respectively[17].

In recent years, studies have been published on chemical dot thermometers, one of the noninvasive temperature measurement methods. The studies on their use in childhood are quite limited. Mauta L *et al* [9] stated in their study on 200 pediatric patients aged 1 - 13 years that the chemical dot measurement method can be used instead of mercury glass thermometers. Rajee M *et al*[22] compared mercury glass, chemical dot and infrared tympanic measurement methods in their study on 194 cases in the adult emergency service. The study also found that chemical dot thermometers can be used instead of mercury glass and infrared tympanic measurement methods. In our study as well, the closest values to rectal temperature among noninvasive methods were obtained by axillary chemical dot thermometers. The sensitivity and specificity rates obtained by axillary chemical dot thermometers were 85.71% and 88.61%, respectively.

The comfort of the temperature measurement methods is important as well as reliability for emergency service staff. Therefore, the comfort of temperature measurement methods also has been evaluated in the studies. In the study conducted by Allegaert *et al*[6], temperature measurement methods were evaluated subjectively by both the measuring nurses and the children along with their parents. They found that the discomfort score of rectal measurement was higher than the discomfort scores of tympanic, skin and temporal artery measurements performed by infrared methods and that these no-invasive methods produced similar discomfort scores[6]. Similarly, Greenes *et al*[12] found in their study on 304 infants (<1 year) that the discomfort score of rectal temperature measurement was statistically significantly higher than discomfort scores of tympanic membrane and temporal artery measurements. They also reported that

discomfort scores of both noninvasive measurement methods were similar[12]. Also in our study, the discomfort score of RT measurement was statistically significantly higher than those of other noninvasive methods in both febrile and afebrile patients; our results were compatible with the literature. Discomfort scores of the non-invasive methods were equal. Different from these studies, the discomfort scores in our study had a statistically significant difference between the febrile and the afebrile patients. On the other hand, the axillary chemical dot measurement method did not differ in discomfort score compared to other measurement methods.

CONCLUSION

In conclusion, the most reliable and comfortable non-invasive measurement method for emergency service applications, compared with RT (which is accepted as the gold standard method) was AT measurement using a chemical dot thermometer. We conclude that this method may be preferred in situations where invasive methods cannot be applied, especially in Pediatric emergency settings and intensive care units.

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Original Article

Knowledge of Urologists and Neurologists about the Urogenital System Involvement of Multiple Sclerosis?

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ABSTRACT

Objectives: Multiple sclerosis (MS) is a demyelinizing disease of the central nervous system with different clinical signs and findings that progresses with episodes of exacerbation and remission. The urinary system is affected in more than 80% of MS patients, and shows a variety of signs and findings. Our study aims to evaluate all urological symptoms and findings, accompanied by urodynamic findings, in patients monitored due to MS.

Design: Retrospective study

Setting: Department of Urology, School of Medicine, Gazi University, Ankara, Turkey; Department of Urology, Samsun Training and Research Hospital, Samsun, Turkey

Subjects: A total of 73 patients, without differentiating the type of MS, who consulted our clinic between year 2003 and 2011.

Intervention: The physical examination findings, demographic characteristics symptoms, and complications of the patients at the time of consultation were individually investigated. The results of any urodynamic investigations of monitored patients were evaluated. Finally, the treatments and results of all patients are discussed

Main outcome measure: The clinical findings, laboratory findings, and complications and treatment results were assessed

Results: The most frequent complaint was urge urinary incontinence. Additionally, in male patients 37.5% had erectile dysfunction and 12.5% had orgasmic complaints, while 12.2% of female patients described dyspareunia.

Conclusion: While the urogenital complaints' multiple sclerosis causes may negatively affect the quality of life of patients, the complications may cause threats to life at the same time. That is why, multiple sclerosis is a disease that should be known well not only by the neurology experts, but also the urology experts.

KEY WORDS: central nervous system, neurology, urodynamic investigations, urology

INTRODUCTION

Multiple sclerosis (MS) is a demyelinizing disease of the central nervous system (CNS) with different clinical signs and findings that progresses with episodes of exacerbation and remission. Due to demyelinizing plaques observed in the white matter of the CNS, it may affect many systems. The urinary system is affected in more than 80% of MS patients, and shows a variety of signs and findings[1,2]. In the literature, the urodynamic findings of MS patients have been well researched, and the urodynamic findings seen in this patient group are described as detrusor overactivity (DOA), detrusor contraction disorder (DCD), and detrusor sphincter dyssynergia (DSD)[3-5]. This study aims to evaluate all urological symptoms and findings, accompanied by urodynamic findings, in patients monitored for MS.

MATERIALS AND METHODS

We retrospectively investigated the data of 73 patients, without differentiating the type of MS, who has consulted our clinic between year 2003 and 2011, in this study. The physical examination findings, demographic characteristics (age, gender, duration of MS, duration of urinary symptoms, age of MS diagnosis, age of onset of urinary complaints after MS diagnosis), symptoms, and complications (urge urinary incontinence, retention, stress urinary incontinence, frequency, urgency, nocturnal enuresis,

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recurrent urinary infections, erectile dysfunction, retrograde ejaculation, dyspareunia) of the patients at the time of consultation were individually investigated. Patients with symptomatic benign prostate hyperplasia, bladder stones, and/or urethral stricture were excluded. The results of any urodynamic investigations of monitored patients were evaluated. Before urodynamic investigation, patients provided a negative urine culture, and the investigation abided by the standards of the International Continence Society (ICS)[6]. The residual urine amounts of the urethral-uncatheteterized patients were examined ultrasonographically before urodynamic investigation. An isotonic solution with temperature of room degrees was used to fill the bladder using a 6 french(fr) double lumen urethral catheter at 50 ml/min. The bladder was emptied by the catheter, before performing the procedure. Abdominal pressure was measured with a 10 fr intrarectal balloon catheter. Investigation was completed in the supine position, and all patients underwent pressure-flow studies. Finally, the treatments and results of all patients are discussed.

The Statistical Package for Social Sciences (SPSS version 16, Chicago, IL, USA) for Windows was used for calculations. The statistical methods used were descriptive statistics and frequency analysis. Results are expressed as mean ± standard deviation (SD) or median (min-max).

RESULTS

The study included 49 female (67.1%) and 24 male (32.9%) patients, consisting 73 patients in total. When the demographic characteristics of our patient group are investigated, the age was identified as 39 (22-65) years (Table 1). The age of diagnosis of MS was 32 (18 - 61) years, while the average age of onset of urinary complaints was 35.78 ± 10.60 years. While the average duration of MS was 84 (2 - 420) months, the duration of urinary symptoms was 30 (1 - 240) months. Urinary complaints were present in 70 patients (95.8%) (Table 2). The average number of urinary symptoms was 1.4 ± 0.64. Of the 24 male patients, three (12.5%) did not describe any urinary complaints, but applied due to orgasmic complaints. The most frequent cause for application of patients was urgency (58.9%, n = 43). While urgency alone without urge urinary incontinence was observed in 8.16% of women, there was no urgency without urge urinary incontinence in male patients. Urge incontinence was the most frequently identified symptom in both women (55.1%) and men (45.8%). When all patients were investigated, apart from urgency and urge incontinence, the other urinary symptoms were, in order, urinary retention, stress urinary incontinence, frequency, and nocturnal enuresis. The primary complaint of four patients (5.5%), all of whom are women, was recurrent urinary infections after MS diagnosis. Additionally, in male patients 37.5% had erectile dysfunction, while 12.2% of female patients had dyspareunia. Two female patients (4.08%) complained of incontinence during orgasm. While the average bladder capacity of the 45 patients who underwent urodynamic investigation was 352.6 ± 154.7 ml, 13.3% of these patients were normal, 17.8% had detrusor contraction disorders, 20% had DOA + DSD, and 48.9% had only DOA. Within the framework of the patients' clinical and urodynamic findings, anticholinergics, alpha blockers, clean intermittent catheterization (CIC), ephedrine, botox injections, and PDE 5 inhibitors were administered either alone or combined. It was observed that all, but two patients had full or partial benefit from the treatments in the acute period.

Table 1: General characteristics of patients

Variables	Patients
Gender	
Female : N (%)	49 (67.1)
Male : N (%)	24 (32.9)
Age (range)	39 (22 - 65)
Age of MS diagnosis (range)	32 (18 - 61)
Age of onset of urinary complaints after MS Diagnosis	35.78±10.60
Duration of MS (Months)	84 (2-420)
Duration of urinary symptoms (Months)	30 (1-240)

Table 2: Patients complaints and findings at time of application according to gender

Complaint	Female n (%)	Male n (%)	Total n (%)
Urge urinary incontinence	27 (55.1)	11 (45.8)	38 (52.0)
Retention	21 (42.8)	9 (37.5)	30 (41.1)
Stress urinary incontinence	8 (16.3)	1 (4.16)	9 (12.3)
Frequency	3 (6.12)	2 (8.3)	5 (6.8)
Urgency	33 (67.3)	10 (41.6)	43 (58.9)
Urgency without urge Incontinence	4 (8.16)	-	4 (5.5)
Nocturnal enuresis	2 (4.08)	1 (4.16)	3 (4.1)
Recurrent urinary infection	4 (8.16)	-	4 (5.4)
Erectile dysfunction	-	9 (37.5)	-
Retrograde ejaculation	-	3 (12.5)	-
Dyspareunia	6 (12.2)	-	-

DISCUSSION

MS is a frequently observed disease that progresses with attacks, affects different levels of the CNS, and may affect the genitourinary system[7,8]. The etiology is not exactly known, but autoimmune mechanisms are blamed[9]. Though the etiology is not clear, the urogenital system is frequently affected, and is known to cause significant mortality. When examined from this point of view, MS is a disease that should be known well not only by neurology experts, but also

by urology experts. Similarly, neurology experts, who primarily monitor MS patients should know the urogenital symptoms, and findings of the disease enough to consult to urologists before the urogenital deterioration has occurred.

When the cause of complaints or symptoms are examined in the literature, the most frequent urinary symptom of MS patient groups is reported as urgency[10-12]. In our study, supporting this data, urgency was identified as the most frequent complaint (58.9%, n = 43). In our patient group, urge urinary incontinence was observed to be the second most frequent urinary symptom (52%, n = 38). While urge incontinence without urgency was not found in male patients, urgency alone was found in only 8.16% of female patients. When examined from this point of view, urge incontinence as a symptom appears to be a more serious problem for this patient group. Our findings are found compatible with the literature in terms of urinary incontinence and irritative voiding symptoms as the dominant complaints[4,13-15]. We also found that symptoms such as nocturnal enuresis, retrograde ejaculation, erectile dysfunction, and/or dyspareunia are frequently seen in our MS patients group, different from the literature. While two female patients describing nocturnal enuresis additionally had urinary incontinence, a male patient applying with the same complaint had no other urinary complaints. Two female patients with different complaints described their urinary incontinence during coitus as the dominant complaint. While one patient additionally described urgency, the other patient described slight urge urinary incontinence leaks during the day. On urodynamic investigation of both patients, DOA was identified and anticholinergic treatment resolved their complaints.

MS does, not only affect the urinary system, but also the sexual functions of patients[16-18]. Apart from the sexual problems developing linked to urinary incontinence mentioned above, six women (12.24%) described dyspareunia. When the literature is investigated, sexual problems in MS patients are mainly caused by dissatisfaction with the relationship, even with a healthy partner. The primary sexual problems related to MS in women is libido loss, and in men are libido loss, erectile dysfunction, and orgasmic complaints[16,19]. In our patient group, while ED was found in 37.5% of male patients, 12.5% of male patients had orgasmic complaints. In our female patients, dyspareunia was identified as the leading sexual complaint. In the literature, among the causes of sexual dysfunction in female MS patients, pain is described as a secondary cause. However, together with pain in this patient group, psychosocial disorders linked to MS may develop, and it should not be forgotten that these may negatively affect sexual functioning. Another interesting point is that, only two male patients with ED complaint accepted the recommended treatment, and used PDE-5 inhibitors. Both patients benefitted from treatment. Of the three patients with orgasmic complaints, one accepted the treatment recommendation and though benefitting from pseudoephedrine treatment, left treatment due to side effects. Within the framework of the symptoms and findings of the 73 patients applying or consulting our clinic, 45 (61.64%) underwent urodynamic investigation. In the literature, urodynamic investigation of MS patients report 25 - 66% DSD, 6 - 29% detrusor contraction disorder, and 27 - 45% DOA[5,7,10,15,20,21]. In our patient group with urodynamic investigation, 48.9% only had detrusor over activity. In the literature, generally the dominant urodynamic finding is DOA, similar to our findings. This patient group was given cholinergic treatment. DOA together with DSD was found in 20% of patients given urodynamic investigation. This patient group was given anticholinergic treatment together with CIC, and some patients were given anticholinergic treatment with alpha blocker treatment. In the same patient group, in accordance with the literature, the rarest finding was detrusor contraction disorder at 17.8%. CIC was the chosen treatment approach for this patient group. None of our patients required permanent urethral catheterization after evaluation. Apart from two patients, in the acute period all patients had full or partial benefit from our treatment approaches. Of the two patients who did not respond to treatment, one had urge incontinence, and the other was a male patient describing stress urinary incontinence.

In our patient group, there was no clear correlation between the patients' symptoms and urodynamic findings. Awad *et al* found a correlation between symptoms and urodynamic findings. Contrary to this Nakipoglu *et al*. reported no correlation[10,22]. When examined from this aspect, urinary symptoms and findings alone may be insufficient to evaluate patients. Urodynamic investigation appears to be a required investigation to be completed when necessary for the MS patient group.

CONCLUSION

MS is a frequently observed disease that affects the urinary system. While the urogenital complaints' causes may negatively affect the quality of life of patients, the complications may be life threatening. Clinical findings alone are not sufficient to evaluate MS patients, and detailed urological and urodynamic investigation may be required. With this point of view, it is necessary to question MS patients about the urogenital system from the moment of first diagnosis.

As a result, it is important that neurology experts know urogenital symptoms and complications, and that urology experts play an effective role in patient monitoring, to ensure both survival and quality of life for patients.

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Conflict of interest: Lokman Irkilata, Metin Onaran, Ali Furkan Batur, Mustafa Ozgur Tan, Ilker Sen declare that they have no conflict of interest.

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Original Article

Propofol Effect-Site Concentration, Bispectral Index and Spectral Entropy as Guides for Propofol Sedation during Spinal Anesthesia

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ABSTRACT

Objective: To study the correlation between, propofol effect-site concentration (Ce prop), Bispectral Index (BIS) and Spectral entropy (state/response, SE/RE), as well as to investigate their threshold values best to detect the desired level of propofol sedation, during spinal anesthesia.
Design: Observational study
Setting: King Fahad Hospital of Dammam University-Saudi Arabia
Subjects: Thirty patients scheduled for total knee replacement under combined spinal epidural anesthesia
Intervention(s): After spinal anesthesia, propofol sedation using target-controlled infusion (TCI) was started at 0.5 μg/ ml and increased incrementally by 0.5 μg/ml. Depth of sedation was evaluated, as well as, BIS, SE and RE every 5 min after each Ce prop equilibrium.
Main outcome measure(s): The correlation between BIS, SE, RE, and Ce prop with different level of sedation score. Also the cut off values of BIS, SE, RE, and Ce prop best to detect the desired level of sedation.
Results: The changes of Ce prop significantly correlated with the changes of BIS, SE and RE values. All are significantly correlated with the changes in the Observer's Assessment of Alertness and Sedation (OAA/S) score. The cut-off values for Ce prop., BIS, SE and RE corresponding to the desired OAA/S score were, 1μg/ml, 75, 75 and 85 respectively, with SE showed significant higher specificity at the level of 100% sensitivity.
Conclusion: During spinal anesthesia under propofol sedation, BIS, SE, RE and Ce propofol were equally correlated with OAA/S score. At 100% level of sensitivity, SE showed the highest specificity, whereas the Ce propofol had the lowest specificity to detect the desired level of sedation.

KEY WORDS: anesthetic procedure, depth of sedation, regional anesthesia, sedative drugs, surgery

INTRODUCTION

Regional anesthesia is a commonly used technique in orthopedic procedures. It offers several advantages. However, Stress factors in operating room may contribute to patient's discomfort, anxiety and restlessness[1]. Sedation is the easiest way to prevent such situations as well as to offer some amnesia for the block procedure and surgical operation[2]. Previous studies have shown that spinal anaesthesia *per se* may have sedative properties[3, 4]. Therefore, there is a possibility of over sedation, even with routine doses of sedatives, with potential respiratory and cardiovascular depression. Thus, appropriate monitoring of depth of sedation remains important issue during spinal anesthesia[5]. The Observer's Assessment of Alertness and Sedation (OAA/S) score is a well-established evaluation of several sedative drugs[6]. However, the OAA/S score requires clinician interaction with subjects and thus frequently disturb the patient's comfort and compromise the already well established sedation[7]. In daily clinical practice, processed, non-invasive, EEG monitors such as the bispectral index (BIS) or spectral entropy (SE & RE) are increasingly used, as objective sedation scales to replace the conventional subjective scores[8-10]. These monitors provide a single numerical value ranging from 100 (fully awake) to zero (deepest level of sedation), and they are now well established to predict loss of consciousness (LOC) and to estimate the

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depth of sedation in surgical patients[11, 12]. Propofol is frequently used as an IV sedative agent during regional anesthetic procedures, as it has a quick onset and offset of action with easy arousability[13, 14]. Lower doses of propofol as sedative also produces amnesia and anxiolysis[13]. The proper sedative doses of propofol for some invasive procedure have been investigated[8-11]. However, its optimal sedative dose during spinal anaesthesia for orthopedic surgeries not yet well investigated. The aim of this study was to investigate the correlation between the values of BIS, SE, RE, and the propofol effect-site concentrations (Ce) with different level of sedation score. In addition to test the sensitivity and specificity of these monitors as predictors of the desired level of sedation during orthopedic surgeries under spinal anesthesia.

SUBJECTS AND METHODS

Following approval of Research and Ethics Committee, University of Dammam and written informed consent, American Society of Anesthesiologists physical Status I and II patients scheduled for elective total knee replacement surgery under combined spinal-epidural anesthesia were prospectively enrolled in the study. Exclusion criteria included; a body mass index (BMI) >35, contraindications for spinal anesthesia, neurological or psychiatric disease, recent administration of sedative, opioid or central nervous system-active drugs and impairment of renal, hepatic, cardiac or respiratory function.

All patients were fasted over eight hours and were not premedicated. In the operating room and prior to the procedure, an intravenous 18 - 20 gauge cannula was placed and all patients received 0.9% NS 10 mL.kg-1 for pre-hydration. Routine monitoring including an electrocardiogram, pulse oximetry and non-invasive blood pressure were fixed and initial values of mean arterial pressure (MAP), heart rate (HR) and oxygen saturation (SpO_2) were recorded. The anaesthesia machine with resuscitating facilities was kept ready for use in emergency. Under aseptic conditions, combined spinal-epidural block was performed by staff-grade anesthesiologists, using a standard midline approach in the sitting position at the L3-L4 or L4-L5 intervertebral space. A dose of 12.5 mg hyperbaric bupivacaine (Marcaine Spinal Heavy; Astra Zeneca, Lund, Sweden) was injected into the subarachnoid space and the epidural catheter was threaded into the same space. Patient lied down immediately and 5 L/ min of oxygen was provided to patients via an oxygen mask which has also a CO_2 sampling tube connected to CO_2 analyzer for measuring end tidal carbon dioxide tension ($EtpCO_2$). MAP, HR, SpO_2, and $EtpCO_2$ were documented immediately after spinal block and every 5 min thereafter until arousal of the patient.

After preparation of the skin of the forehead and both the temples of the patient using alcohol solution, the four electrodes of BIS (Aspect Medical System, MA, USA) and the three electrodes of entropy (GE Healthcare, Helsinki, Finland) were placed on the patient's forehead as recommended by the manufacturers. The side of electrode placement (left or right temporal) was chosen at random. Patients were instructed to close and open their eyes when the investigator called their name and shook their body to determine the OAA/S score from 5 - 0 (Table 1). Baseline values for the BIS, RE and SE were recorded before propofol infusion.

Table 1: Observer's assessment of alertness/sedation scale

Description	Sedation level
Responds readily to name spoken in normal tone	5
Responds lethargically to name spoken in normal tone	4
Responds only after name is called loudly, repeatedly, or both	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

Sensory block level was evaluated by the pin-prick test using 25 G needle. As soon as the level of sensory block reached T10 dermatome, the operation was started and at the same time, propofol sedation was initiated.

Propofol was administered using a computer-assisted, target controlled infusion (TCI) device (Orchestra TM and Base ATM, Fresenius Vial Infusion Systems, France) which uses Schneider's pharmacokinetic model[15]. Initially, the target effect-site concentration of propofol (Ce prop) was set to 0.5 μg/ ml and increased incrementally by 0.5 μg/ ml. After each 0.5 μg/ ml increase, equilibration between plasma and Ce prop (as recorded on the screen of the syringe driver), was awaited and was kept unchanged for 5 min. Subsequently, the next higher effect-site concentration was targeted.

Ten seconds before each increase in Ce prop, the values of BIS, SE, RE, Ce prop as well as the depth of sedation (using the 5 - 0 points OAA/S scale) were recorded by a blind observer (blind to the study design). The sequence of testing was always the same, first the electronic indicators, then the OAA/S score. Our target level of sedation was to achieve moderate sedation (patient responds properly to verbal or light tactile stimulation) i.e. OAA/S score 3 or 2. After achieving our goal of sedation, the study was continued until OAA/S score of one (responds only after painful trapezius squeeze) and then, terminated. After conclusion of the study the propofol effect-site concentration was reduced to the concentration corresponding to our targeted level of sedation.

Our primary outcome was to study the correlation between the values of BIS, SE, RE, and the propofol effect-site concentrations with different level of sedation score. Our secondary outcome was to determine the cut off values of BIS, SE, RE, and Ce prop, which enabled to detect the desired level of sedation, and to compare the sensitivity and specificity of these parameters as indicator of our targeted level of sedation.

Statistical analysis

We used descriptive statistics to calculate the mathematic means (SD) of demographic, surgical and other clinical continuous data and to calculate the median (range) of the degree of patient's and surgeon's satisfactions. The correlations between the change of Ce prop and the changes of BIS, RE and SE values and as well as the changes of OAA/S score were determined using regression test.

We calculated cut-off (threshold) values of the Ce prop, BIS, SE and RE with the best level of discrimination to detect an OAA/S score of 2 or 3 (the desired level of sedation) using Receiver Operating Characteristic (ROC) curve analysis. From the pilot study, we noticed that at the same level of Ce prop, patients displayed different levels of sedation depth. So we expected a 25% reduction of Ce prop specificity than SE at the point of 100% sensitivity (no false-negatives) at ROC curve. Thus a sample of 30 subjects was needed to achieve a significance level of 0.05 with power of 80%. We used MedCalc statistical program version 12 (MedCalc Software bvba, Mariakerke, Belgium) for assessment.

Table 2: Demographic, operative and surgical data.

Data	Values
Age (years)	60.9 ± 4.9
Weight (kg)	81.9 ± 3.3
Height (cm)	161 ± 1.1
BMI (kg/m2)	30.4 ± 0.28
Gender (Male/female)	12/18
Duration of surgery (min)	149.6 ± 2.4
Patient satisfaction	3 (2 - 3)
Surgeon's satisfactions	3 (2 - 3)

The values are means (SD), median (range) or ratio; BMI = Body mass index

RESULTS

Thirty patients were enrolled in this study. No patients were excluded and Table 2 shows the patient and surgical characteristics of the study population. All patients had satisfactory anesthesia and completed their surgeries without general anesthesia or analgesic supplementation.

All patients showed hemodynamic stability throughout the study period without significant hypotension or bradycardia (30% below the initial values). Although $EtpCO_2$ was significantly increased with high Ce prop, it remained within normal range throughout the study.

The changes of propofol effect-site concentrations significantly correlated with the changes of BIS, SE and RE values (Fig 1) with Correlation coefficient = 0.9924, 0.9929 and 0.9925 respectively with P-value <0.001. All of these four monitors (Ce prop, BIS, SE and RE) showed significant correlation with

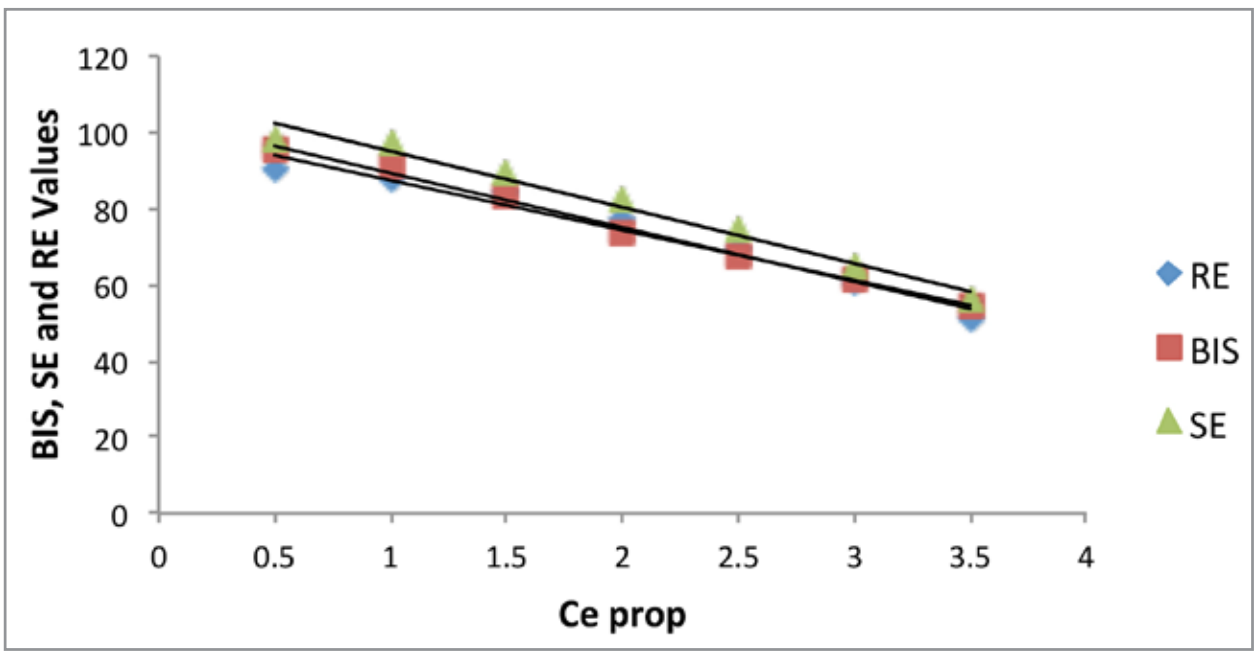

Fig. 1: Correlation between changes of Propofol effect-site concentration with the changes of Bispectral Index, response entropy, and state entropy.

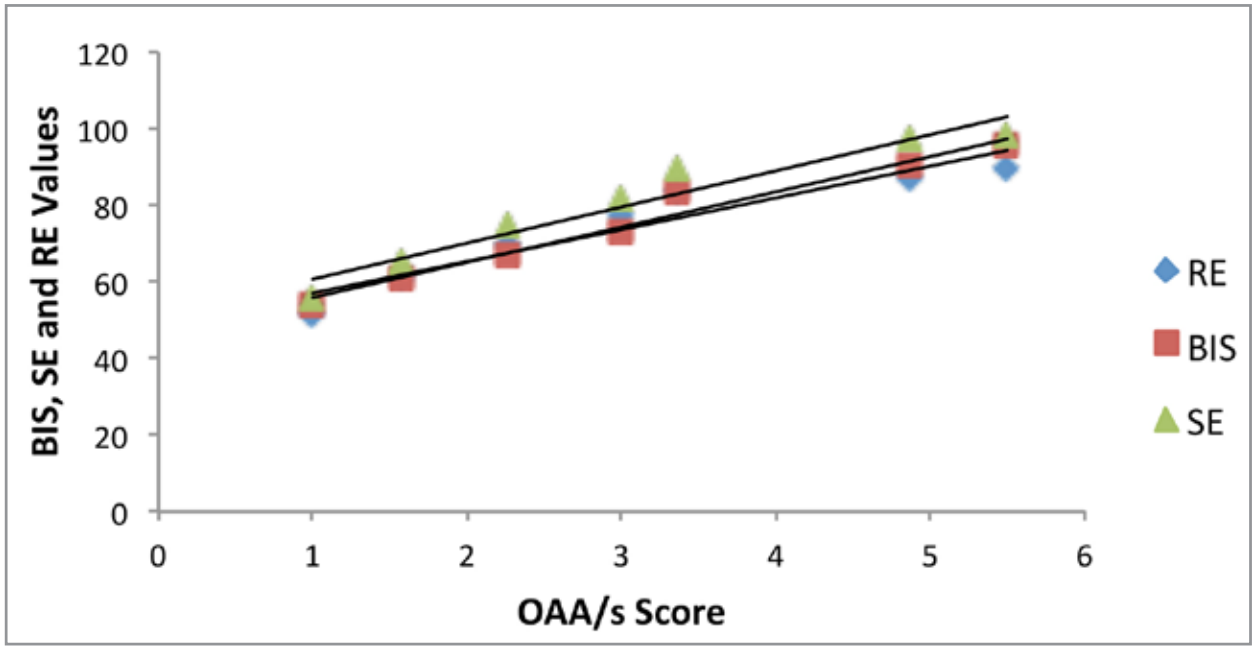

Fig. 2: Correlation between changes of Bispectral Index, state entropy and response entropy versus different levels of Observer's Assessment of Alertness and Sedation score.

the changes in the OAA/S score (Fig 2 and 3) with Correlation coefficient equal to 0.9889, 0.9932, 0.9763 and 0.9848 respectively with P-value <0.001 and without any significant difference between the four monitors.

The sensitivity/specificity analysis of ROC curves (Fig 4) showed that the cut-off (threshold) values for Ce prop, BIS, SE and RE at the point of maximum combined sensitivity/specificity, with the best ability to detect an OAA/S score of 2 or 3 during propofol sedation were, 1, 75, 75 and 85 μg/ml respectively, with no significant differences between their areas under ROC curves (Table 3). At the level of 100% sensitivity, SE showed significant higher specificity compared with other monitors (Table 2), whereas the Ce propofol had the lowest specificity.

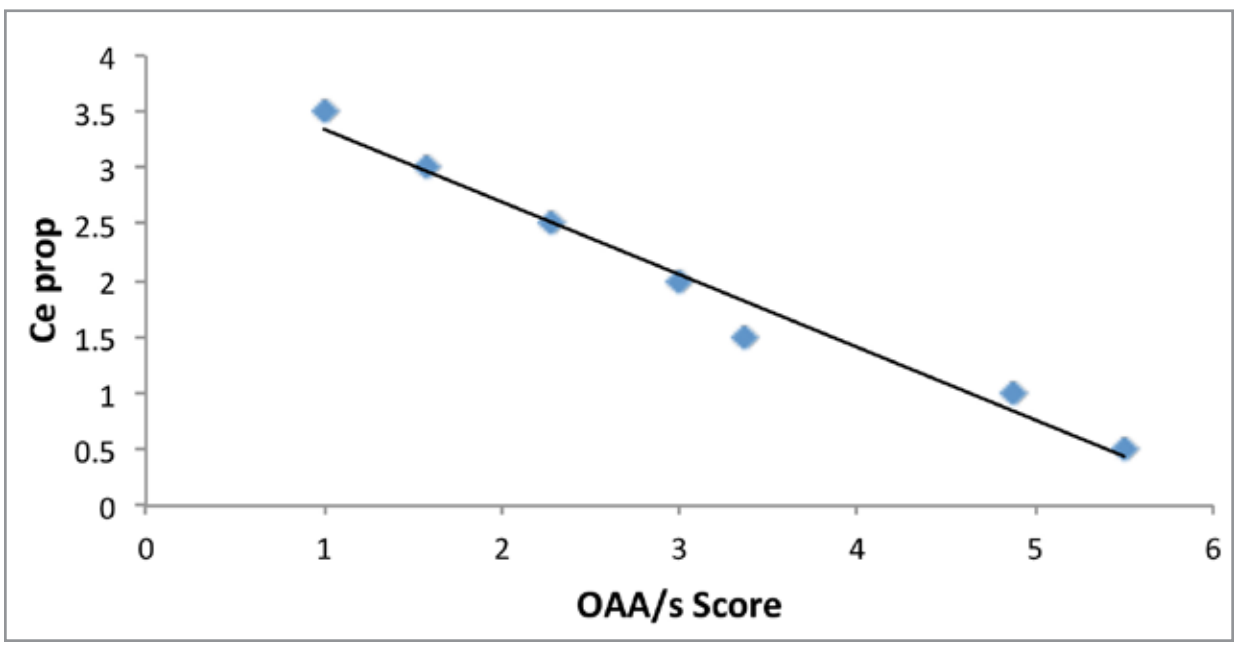

Fig. 3: Correlation between changes of Propofol effect-site concentration versus different levels of Observer's Assessment of Alertness and Sedation score.

Table 3: Data of ROC curve analysis

Monitor	Cut-Off value at high (Sens. + spec.)	Sensitivity (95% CI)	Specificity (95% CI)	Cut-off value at 100% sensitivity	Specificity at 100% sensitivity (95% CI)	AUC (95% CI)
Ce prop (μg/ml)	1 (μg/ml)	89.5 (80.3 - 95.3)	69.50 (60.3 - 77.6)	0.5 (μg/ml)	50.85 (41.5 - 60.2)	0.740 (0.672- 0.800)
SE value	75	100 (95.3 – 100)	71.19 (62.1 - 79.2)	75	71.19 (62.1 - 79.2	0.743 (0.676 - 0.803)
RE values	85	100 (95.3 - 100)	61.02 (51.6 - 69.9)	85	61.02 (51.6 - 69.9)	0.742 (0.675 - 0.802)
BIS values	75	94.74 (87.1 - 98.5)	67.80 (58.6 - 76.1)	80	61.02 (51.6 - 69.9)	0.748 (0.681 - 0.808)

Sens. = sensitivity; spec. = specificity; 95% CI = 95% confidence interval; AUC = Area under the curve

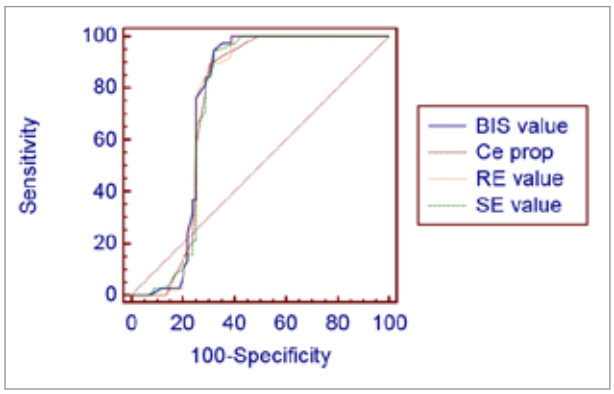

Fig. 4: Multiple receiver operating characteristic (ROC) curves obtained from Ce prop, BIS, SE, and RE to detect OAA/S score of 2 or 3 during propofol sedation.

DISCUSSION

In this study, we demonstrated an equal significant correlation of BIS, SE and RE values with the changes of Ce prop. The progressive increase of Ce prop and the associated gradual reduction of BIS, SE and RE values were all significantly correlated with the changes in the depth of sedation (OAA/S score). From the ROC curve analysis, the cut off values of Ce prop, BIS, SE, and RE which were able to detect the desired level of sedation, were 1, 75, 75 and 85 μg/ml respectively with significant higher specificity with SE when compared with the other three monitors at 100% sensitivity.

To our knowledge, our study is the first study investigated whether Ce prop is a reliable guide for propofol sedation during spinal anesthesia. In agreement with previous studies[16-19], our results showed strong correlation of BIS, SE and RE with the level of propofol sedation and confirmed their reliability to guide the level of sedation during spinal anesthesia and other invasive procedures. On the other hand, although Ce prop showed strong correlation with OAA/s score in our study, it showed a significantly very low specificity at 100% sensitivity, as detector of the desired level of sedation compared to BIS and Entropy. This finding confirmed the results of Kwon M *et al*[20] who stated that the Ce prop should not guide the sedation depth alone, because at the same level of Ce prop, patients displayed different levels of sedation depth in the conventional OAA/S scale and entropy monitoring.

As there were no significant difference in the correlation of the four monitors (Ce prop, BIS, SE and RE) with OAA /s score, we used the ROC curve analysis to calculate the behavior of the four monitors at the two important points of the ROC curves, at the highest sum of sensitivity and specificity (the most commonly used cut off point) and at the level of 100% sensitivity (*i.e*. no false-negatives). The four monitors did not show significant differences in their behavior at the level of combined sensitivity/specificity. In contrast, at the level of 100% sensitivity, SE showed a significantly better specificity compared to other monitors. Our results are similar to the results of Schmidt *et al*[18] and Vakkuri *et al*[19] who showed that the SE index correlated better with sedation levels compared to BIS and with the results of Iannuzzi M *et al* [21] who reported SE appeared to be more useful than BIS in predicting both LVC (loss of verbal command) and LOC (loss of consciousness) during propofol anesthesia.

Although previous studies have shown that spinal anaesthesia *per se* may have sedative properties[3, 4], we did not observe any sedation before the start of propofol infusion. Morley and colleagues[22] have also shown that in unsedated patients, neither epidural nor spinal anesthesia produce clinically detectable sedation. This is because, the previous study[4] investigated volunteers in a darkened room with soft music, in contrast with the unpremeditated patients with preoperative anxiety in a noisy orthopedic operating room in our study.

In this study, we did not use opioid sedative combined regimens, because previous studies reported inability of EEG-derived monitors to detect the opioid extra-cortical sedative effect[23]. Additionally, Hernández-Gancedo *et al*[24] reported an overlap of entropy values corresponding to different levels of Ramsay sedation score. They recommended more sophisticated objective measures capable of measuring all sedation depths produced by the opioid synergistic effect of reinforcing sedation.

Limitations

One limitation of our study was that, it was conducted in elderly patients who might have expected some degree of hearing loss and the observers consequently, might have used more intense verbal stimuli. However, we have overcome this problem by assigning a single investigator to perform all assessments to minimize inter-observer variability. Second limitation was that, we used the ROC cure analysis to detect two levels of OAA/s score (2 and 3) as one unit (positive finding), which could affect the accuracy of the cut-off points and resulted in relatively low specificity for all monitors. However, the use of one level of OAA/s score as a target level of sedation is not clinically accepted.

CONCLUSION

As monitors of propofol sedation during spinal anesthesia, BIS, Spectral Entropy and Ce propofol were equally correlated with OAA/S score. Studying their ROC curves at the 100% level of sensitivity, State Entropy showed the highest specificity in detecting the desired level of sedation, whereas the Ce propofol had the lowest specificity and should not be used as a principle guide of propofol sedation.

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Original Article

CHADS2 Scores for Stroke Prediction in Patients with Chronic Hepatitis C Infection

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ABSTRACT

Objective: To investigate whether CHADS2 score, which is composed of congestive heart failure (C), hypertension (H), age (A), diabetes (D), and stroke (S) could help to predict strokes in hepatitis C virus (HCV) carriers in Taiwan.
Design: Retrospective cohort study using the database between the period of 2002 and 2009 from the Taiwan National Health Insurance Program
Setting: Taiwan National Health Insurance Program, Taiwan
Subjects: Seven thousand three hundred eighty-one patients with chronic HCV infection were enrolled and the CHADS2 score was calculated for each individual.
Main outcome measures: The incidence rates of strokes in these patients
Results: CHADS2 scores, 0 - 2, 3 and over 4 were found to respectively correspond to stroke rates of 0.1%, 18.6% and 35.5%, indicating a significantly strong correlation between CHADS2 score and stroke in patients with chronic hepatitis C infection (AUC = 0.97). Compared to CHADS2 scores 0 - 2, the adjusted respective hazard ratios for scores of 3 and 4 or above are 80.52 and 170.41.
Conclusions: It is a serious concern not only of advanced liver disease but also stroke for patients with chronic hepatitis C infection. The CHADS2 score can be applied to evaluate the risk of ischemic stroke in hepatitis C carriers.

KEYWORDS: cirrhosis, chronic HCV, heart failure, hepatocellular carcinoma, stroke

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease. Globally, an estimated 130 - 150 million people suffer chronic HCV infection worldwide and hepatitis C-related liver disease claims between 350,000 and 500,000 lives annually[1]. Complications from cirrhosis caused by chronic HCV infection are the main indication for liver transplantation in the United States and Europe, making the virus an important public health and economic issue.

The rate of persistent viremia after acute HCV infection ranges from 55% to 85%, leading to chronic infection. However, results for chronic infection with HCV are quite heterogenic between individual, ranging from minimal liver parenchymal change to progressive fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The risk of developing cirrhosis ranges from 5% to 25% over periods of 25 to 30 years[2,3]. Once the patient is diagnosed with HCV related cirrhosis, HCC develops in 1 - 3% per year[4,5].

Cerebrovascular disease is the second leading cause of death worldwide, leading to 6.7 million deaths in 2012[6]. It has remained a great health burden in most industrialized countries during the past decade and in the future. Although several understanding risk factors

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for stroke have been established[7], some infectious pathogens, including HCV, might contribute to the occurrence of the disease[8-10].

The CHAD2 score is calculated by awarding points for congestive heart failure (C), hypertension (H), age (A), diabetes (D), and stroke (S). The measure is now widely used to evaluate the risk of cardiovascular events in patients with atrial fibrillation and to determine indications of anticoagulant therapy[11]. Previous studies have extended the use of CHADS2 score to evaluate risk of cardiovascular events in patients other than atrial fibrillation[12].

In this study, participants with HCV antibody seropositivity were adopted from the National Health Insurance research database (NHIRD) of Taiwan. This database enrolls up to 99% of the 23 million residents of Taiwan who receive medical care through the National Health Insurance (NHI) program which consists of ambulatory and inpatient care records and the registration files of the insured. The aim of this study was to investigate the predictive value of CHADS2 score on cardiovascular events in HCV carriers.

SUBJECTS AND METHODS

Study population: This observational study was conducted using a retrospective cohort of the Taiwanese population from 2002 to 2009, enrolled in NHIRD in Taiwan. The Bureau of National Health Insurance of Taiwan randomly reviews the charts of one out of every 100 ambulatory cases and one out of every 20 inpatient cases; it also performs patient interviews to verify the diagnosis accuracy. This study recruited patients ≥18 years of age diagnosed with HCV infection (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, V02.62) between the years 2002 and 2009.

Risk score calculation: CHADS2 scores were calculated for each patient by giving each, one point for the presence of congestive heart failure, hypertension, age older than 75 years, and diabetes and two points for a history of stroke or transient ischemic attack (TIA). The study patients were divided into three groups by their CHADS2 scores: 0 - 2, 3, and ≥4.

Study end point and patient follow up: Stroke events covering the years from 2002 to 2009 were collected to calculate the cumulative rate of stroke in each group. Administrative data was used to track each patient for five years from the time of their first diagnosis of HCV infection to identify stroke events during the study period.

Statistical analysis

Data analysis was conducted using SPSS (version15, SPSS Inc., Chicago, IL, USA). The receiver operating characteristics curve was used to assess the prediction accuracy for stroke by using the CHADS2 score to present plots of observed and predicted stroke events. The cumulative rates of stroke events were estimated using the log rank test between different groups among HCV carrier patients. The Cox proportional hazards regression model was used to compare the outcomes between different risk groups. We calculated hazard ratios (HR) along with 95% confidence intervals (CI) using a significance level of 0.05. A two-sided p-value ($p < 0.05$) was used to determine statistical significance.

RESULTS

A total of 7381 patients were diagnosed with HCV antibody seropositivity from 2002 to 2009 within the NHIRD. Table 1 summarizes the number of patients, age, gender, and different CHADS2 score group distributions. The mean age at diagnosis was 54 ± 14 years and 53.1% of patients were male. The mean CHADS2 score was 0.59 ± 0.9. The mean CHADS2 score is 0.57 ± 0.91 in male and is 0.60 ± 0.90 in female. There is no difference in the risk of stroke between males and females (*P*-value = 0.143,Table 2). Severe comorbidity (CHADS2 score ≥3) was noted in 4.3% in all hepatitis C patients. We further subdivided the hepatitis C patients into three groups based on their CHADS2 scores (Table 2). The average incidence rate

Table 1: Baseline characteristics of the patients with hepatitis C from 2002 to 2009 in Taiwan (n = 7381)

Variables	Study population N (%)
Total	7381
Mean age, years(±SD)	54 ± 14
CHADS2 score	
Mean±SD	0.59 ± 0.90
0-2	7066 (95.7)
3	194 (2.6)
Over 4	121 (1.6)
Gender	
Male	3923 (53.1)
Female	3458 (46.9)
Comorbidities	
Hyperlipidemia	305 (4.1)
Chronic kidney disease	182 (2.5)
Coronary artery disease	294 (4.0)
Atrial fibrillation	28 (0.4)
Use drug	
Clopidogrel drug	185 (2.5)
Aspirin drug	914 (12.4)
Socioeconomic status (SES)	
Low SES	2977 (40.3)
Moderate SES	3111 (42.1)
High SES	1293 (17.5)
Urbanization	
Urban	1658 (22.5)
Suburban	3188 (43.2)
Rural	2535 (34.3)
Geographic region	
Northern	2496 (33.8)
Central	1465 (19.8)
Southern	3169 (42.9)
Eastern	251 (3.4)

Table 2: The cumulative rate of stroke in difference CHADS2 score from 2002 to 2009 (n = 7381)

Variables	n	Case (%)	p-value
CHADS2 score			<0.001
0 - 2	7066	9 (0.1)	
3	194	36 (18.6)	
Over 4	121	43 (35.5)	
Mean ± SD			0.143
Male	0.57 ± 0.91		
Female	0.60 ± 0.90		

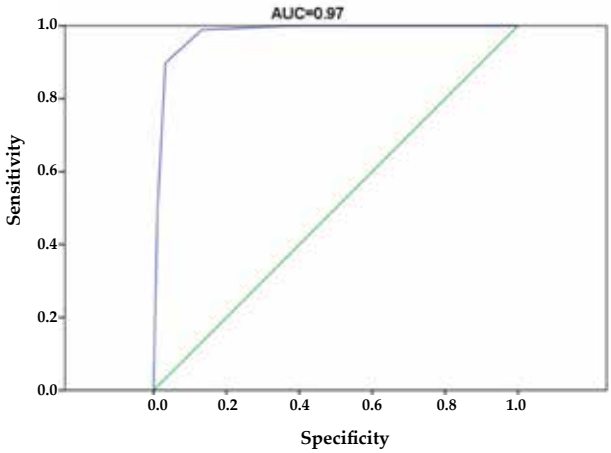

Fig 1: Receiver operating characteristics curve for CHADS2 in prediction of stroke in hepatitis C patients.

of stroke was found to be 0.1%, 18.6% and 35.5%, respectively, for CHADS2 scores of 0 - 2, 3 and over 4 (p <0.001).

Fig 1 shows that the c-statistic was 0.97. Fig 2(a) shows the Kaplan-Meier cumulative risk of stroke curves. Hepatitis C patients with higher CHADS2 scores were more likely to suffer stroke events (p <0.001). Hepatitis C patients with a score of ≥3 are associated with the higher rate in stroke (Fig 2(b), p <0.001). In multivariate analysis, further adding CHADS2 score is associated with a 4.19-fold (95% CI, 3.45 - 5.08) increased risk for stroke when CHADS2 score is a continuous variable (Table 3, model A). In Table 3, model B, while CHADS2 score is an ordinal variable and divided into three groups, higher CHADS2 scores remained an independent prognostic factor for the risk of stroke, with hazard ratios of 80.52

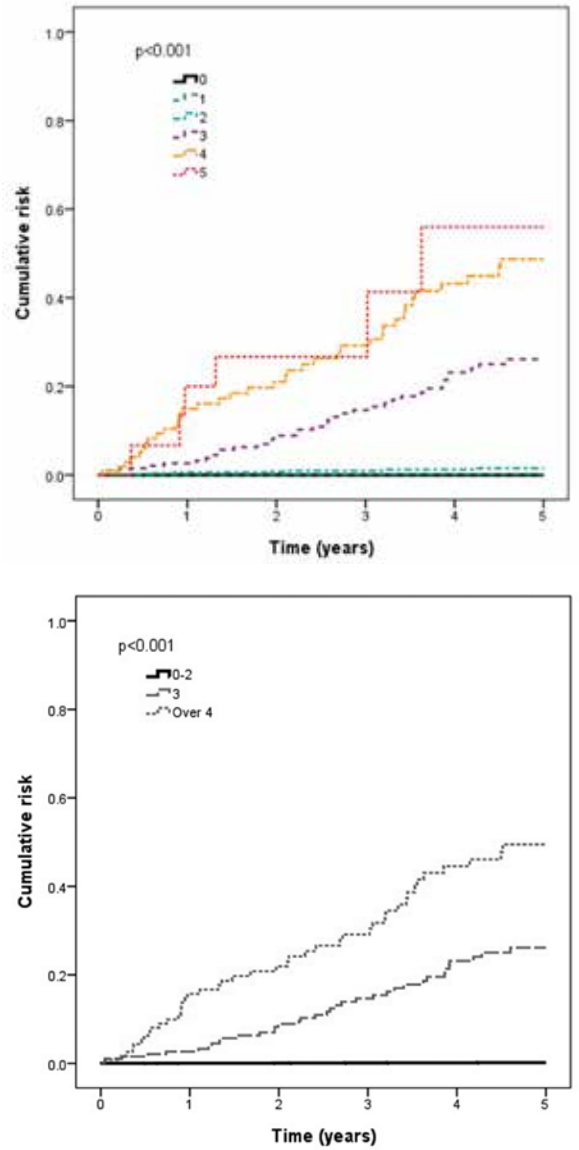

Fig 2 (a): Stroke risk stratified by CHADS2 score. **(b):** Stroke risk stratified by CHADS2 score categories

(95% CI, 36.12 - 179.48) and 170.41 (95% CI, 76.14 - 381.40) in CHADS2 scores of 3 and over 4, respectively, compared to a CHADS2 score 0 - 2 after adjusting for other factors.

Table 3: Hazard ratios of individual CHADS2 score for stroke in patients with hepatitis C

Score	Adjusted HR	Model A* 95% CI	p-value	Adjusted HR	Model B** 95% CI	p-value
CHADS2 score	4.19	3.45 - 5.08	< 0.001			
0 - 2	.....	.....	.....	1	.....	.....
3	.....	.....	.....	80.52	36.12 - 179.48	0.790
Over 4	.....	.....	.....	170.41	76.14 - 381.40	< 0.001

Adjust for the patients' age, gender, aspirin drug, clopidogrel drug, socioeconomic status, urbanization, geographic region and comorbidity
Model A*: CHADS2 score as continuous variable; Model B**: CHADS2 score as ordinal variable

DISCUSSION

Patients with HCV infection may have extrahepatic manifestations, or these manifestations may occur in patients known to have chronic hepatitis C. These extrahepatic manifestations associated with HCV infection are classified into various categories according to the level of evidence, supported by epidemiological studies, pathogenetic studies, or various observations[13]. Some of these associations may need further confirmation.

A community-based prospective cohort study in Taiwan demonstrated the association between HCV infection and cerebrovascular diseases[8], reporting 255 cerebrovascular deaths during 382,011 person-years of follow-up. The reported hazard ratio of cerebrovascular death was 2.18 (95% CI, 1.50 - 3.16) in patients with HCV infection versus those without HCV infection. Elevated serum HCV RNA levels were associated with an increasing risk of cerebrovascular death. Even anti-HCV-seropositives with undetectable serum HCV RNA increased stroke risk compared with anti-HCV-negatives. A recent meta-analysis of four retrospective studies suggested that HCV infection increased the risk of stroke[14]. The pooled odds ratio for stroke risk with HCV was 1.58 (95% CI, 0.86 - 2.30). The increased risk of cerebrovascular events in HCV patients might be attributed to either cryoglobulinemia, which leads to the thickening of the vessel wall through the deposition of immune complexes or atherosclerosis, which is provoked by inflammatory cascade from the circulation of HCV in serum[8, 9].

The CHADS2 score is used clinically to predict the risk of stroke in patients with atrial fibrillation. It has also been used extensively to evaluate the risk of stroke in patients with and without atrial fibrillation[12, 15-17]. In the present study, we introduce the CHADS2 score could reliably help to predict the risk of stroke in patients with chronic HCV infection (AUC = 0.97).

For decades, interferon-based therapy (IBT) has been the standard of care for the treatment of HCV infection, and achievement of sustained virologic response (SVR) could indicate a permanent cure in the vast majority of patients[18-20]. Once achieving SVR, patients can reduce the development of complications of HCV-related liver and extrahepatic diseases, including liver necroinflammation, fibrosis, cirrhosis, hepatocellular carcinoma and death[21]. Furthermore, a retrospective cohort study in Taiwan was designed to investigate the association between HCV infection and stroke, and whether IBT reduces stroke risk in patients with chronic hepatitis C[10]. Results of the study suggest that HCV-infected patients had a 23% increased risk of stroke compared to those without HCV-infected, and IBT was associated with a 61% reduction of stroke risk in HCV-infected patients. According to the results of studies from Hsu[10], Lee[8] and ours, we could possibly conclude that HCV-infected patients with high CHADS2 score and viral load, may reduce risk of stroke through anti-HCV treatment.

Our study had some limitations. First, the material of this study is retrospectively collected from the NHIRD. The diagnoses of HCV seropositivity and stroke are dependent on ICD codes used in the NHIRD. Second, we could not know other risk factors of stroke among the enrolled patients, such as obesity, smoking and inactivity. Third, the CHADS2 score is easy to use with good predictive value of stroke risk. However, the binary input (yes or no) does not think about the severity and duration of congestive heart failure (C), hypertension (H), and diabetes (D), which would impact the risk of stroke. This is the reason why we enrolled large number of patients in this study to minimize the possible impact. Taiwan's National Health Insurance Bureau has made every effort to verify the diagnosis accuracy based upon random chart reviews and patient interviews. In addition, because the NHI achieves 99% coverage in Taiwan, our study incurs minimal risk of selection bias.

CONCLUSION

Patients with chronic hepatitis C infection are prone to stroke. The same as advanced liver disease, stroke is a major health event in patients with chronic hepatitis C infection. The CHADS2 score is found to have good predictive value to evaluate the risk of ischemic stroke in HCV carriers. Not only in surveillance of advanced liver disease, stroke risk evaluation and management should be applied more aggressively for HCV patients with CHADS2 scores $\geq$3.

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This study was initiated after approval by the Institutional Review Board of Buddhist Dalin Tzu Chi General Hospital, Taiwan (B10302016-2). All identifying personal information were removed before statistical analysis to conform the rules of review board.

Conflict of interest statement: The authors disclose no conflicts of interest.

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Original Article

Outcomes of In-Hospital Cardiopulmonary Resuscitation after Introduction of Medical Emergency Team

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ABSTRACT

Objective: Many countries set up clinical emergency response systems such as medical emergency team, rapid response team. But there are still some problems regarding the benefit, design, and advisability of implementing a clinical emergency response system. The present study evaluated the outcomes of in-hospital cardiopulmonary resuscitation after introduction of the first comprehensive the code blue and medical emergency team (MET) system on cardiopulmonary resuscitation (CPR) attempts in-hospital.
Design: Retrospective study
Setting: Harput State Hospital, Department of Emergency Medicine, Elazig, Turkey
Subjects: All code blue calls applied in this hospital from January 2010 to June 2011were evaluated
Intervention: None
Main outcome measures: Rates of return of spontaneous circulation (ROSC) and survival to hospital discharge after CPR
Results: A total of 264 code blue calls were performed during study period. There were 186 (70.5%) calls required immediately CPR attempt, 50 (18.9%) calls required only medical treatments, 18 (6.8%) drill calls for code blue team and 10 (3.7%) missed calls. ROSC and survival to hospital discharge were 41.4% and 6.4% respectively. Time of arrival at the scene was less than two minutes in 74.7% of code blue calls. ROSC occurred in 88.2% of VT/VF cases. A duration of CPR of less than 15 min was related to better CPR outcomes and ROSC ($p < 0.001$).
Conclusion: Response to CPR attempts is affected by early activation of the code blue system and early response of the MET. Therefore, introduction of MET and code blue systems is required for all hospitals in the world.

KEYWORDS: cardiac arrest, code blue, emergency intervention, intensive care, medical emergency

INTRODUCTION

Advances in modern medicine have led to longer life expectancy and an increase in chronic diseases. As a result, hospitalization ratios, length of stay, number of cases requiring emergency intervention and cardiac arrest (CA) in-hospital have increased. Despite all advances in medicine, the incidence and mortality of CA in-hospital is high[1-3]. The real incidence of in-hospital CA cannot be easily identified due to multi factorial effects related to patients and hospitals. CA incidence is approximately 3.6 - 4.02/1000 in hospitalized patients[4]. An advanced cardiac life support protocol (ACLS) should be used to maintain adequate respiration and circulation for in-hospital patients. Therefore, many countries set up clinical emergency response systems such as medical emergency team (MET), rapid response team, patient-at-risk team and critical care outreach team for cardiopulmonary resuscitation (CPR) and emergency response[5,6]. But there are still some problems regarding the benefit, design, and advisability of implementing a clinical emergency response system[2].

Herein, we retrospectively analyzed the existing solutions and emerging pitfalls of the first comprehensive the code blue and MET system on CPR attempts in-hospital.

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MATERIALS AND METHODS

Study setting

Code blue calls made over an 18-month period in our hospital were evaluated retrospectively. Our hospital has wards with 180-bed, an emergency department with 10-bed, intensive care unit (ICU) with 6-bed, and a coronary care unit (CCU) with 10-bed. An average of 380,000 patients were admitted to the emergency department and clinics, 1350 patients were hospitalized in wards and 215 patients were hospitalized in intensive care units during the study period.

MET design

In January 2010, we established a MET system called Code Blue in hospital. Secondly, a MET including a specialist, a nurse, a wheel stretcher employee and a security officer was created. Lastly, all healthcare providers in our hospital and all members of the MET were trained for basic life support, ACLS and the code blue system by planning an educational course program. In this established MET available 24 hours a day, 7 days a week, the leader is an anesthesiologist or an emergency department physician in day shifts (defined as 8:00 to 15:59) and a specialist (general internist, cardiologist, pulmonary disease specialist, general surgeon, and urologist) in the night shifts (defined as 16:00 to 07:59). A code blue call form is filled out by the MET leader at the end of an event. The MET called Code Blue is activated by pressing a button located up above the nurse's desk. The call button activates a central speaker system which is audible throughout the hospital and specifies the location of an event. There are emergency care kits and biphasic defibrillators in every wing of the hospital and the MET is responsible to arrive at the location of the code blue as soon as possible.

Data collection

Data were collected from code blue call forms including demographic data (date of birth/age and sex), underlying diseases, location of the event, date and time of arrest, event notification time, time of arrival at the scene, the initial cardiac rhythm, the status of patients, duration of CPR, outcome of CPR and end of event.

Patients less than 18 years of age, patients having incomplete or illegible data in code blue call forms and repeated code blue calls were all excluded from the scope of this study. Following an activation of system, calls filled out on the code blue form by the MET leader at location of the event were included in our study.

We defined the return of spontaneous circulation (ROSC) as the presence of a palpable rhythm after 20 minutes of successful CPR.

Statistical analysis

Continuous variables were expressed as means and SD. Categorical data was expressed as a percentage and compared using the chi-square test. Statistical significance was defined as $p < 0.05$. All variables were analyzed by using the Statistical Package for Social Sciences (SPSS v17.0).

RESULTS

We evaluated a total of 264 code blue calls. There were 186 (70.5%) calls required immediately CPR attempt, 50 (18.9%) calls required only medical treatments, 18 (6.8%) drill calls for code blue team and 10 (3.7%) missed calls (Table 1). A total of 78 calls which did not perform CPR were excluded from analysis. This left 186 arrests that required CPR. A total of 109 (58.6%) patients did not achieve ROSC, while 77 (41.4%) patients achieved it after CPR. Five of those patients (6.4%) who achieved ROSC were discharged alive from hospital (Table 2). Fifty calls required only medical treatments, which included 14 (28%) hypotension cases, 10 (20%) tachycardia cases, seven (14%) hypertension cases, nine (%18%) dyspnea cases, six (12%) chest-pain cases, three (6%) syncope and one (2%) convulsion. One (2%) among the fifty patients who required only medical treatments experienced cardiopulmonary arrest subsequently.

Table 1: All code blue calls

Characteristic	Number of calls n = 264 (%)
Received CPR	186 (70.5)
Received only medical treatment	50 (18.9)
Drill calls	18 (6.8)
Missed calls	10 (3.7)

CPR = Cardiopulmonary resuscitation

Table 2: Patients who received cardiopulmonary resuscitation (CPR) following cardiac or respiratory arrest

CPR status	Number of patients n = 186 (%)
Not achieved ROSC	109 (58.6)
Achieved ROSC	77 (41.4)
Survived to hospital discharge	5 (6.4)

ROSC = Rates of return of spontaneous circulation

There were 91 (48.9%) females and 95 (51.1%) males included in our study sample. The average age was 63.8 ± 22.25 for males and 69.3 ± 13.93 for females. ROSC after CPR was not related to age and gender ($p > 0.05$).The characteristics of the code blue calls are shown in Table 3.

Time of arrival was 60 - 90 sec in 72 (27.3%) calls, 90–120 sec in 125 (47.4%) calls and 121 –240 sec in 60 (23.1%) calls, longer than 240 sec in five (%1.9), and

the time was unknown in two calls. Time of arrival at the scene was less than 2 min in 197 (74.7%) code blue calls. A total of 79 (42.5%) calls were received during the day shift, 46 (%58.2) of which had ROSC. A total of 107 (60.3%) calls were during the night shift, 76 (71.1%) of which did not achieve ROSC. The rate of CPR success was significantly lower for the night shift calls (p <0.001) (Table 3).

CA was diagnosed in 98 (58.4%) patients. It was significantly related to unresponsiveness to CPR compared to pulmonary and cardiopulmonary arrests (p <0.05). Malignancy was significantly related to unresponsiveness to CPR (p <0.001). A duration of CPR less than 15 min was related to better CPR outcomes and ROSC (p <0.001). Patients with an initial rhythm of pulseless electrical activity (PEA) had a significantly lower ROSC ratio (p <0.05) (Table 3).

Table 3: The characteristics of the code blue calls

Characteristics	Total n = 186 (%)	ROSC		p -value
		No n = 109 (%)	Yes n = 77 (%)	
Sex				> 0.05
Female	91 (48.9)	53 (58.2)	38 (41.8)	
Male	95 (51.1)	56 (58.9)	39 (41.1)	
Age, years				> 0.05
≥65	106 (52.2)	62 (58.4)	44 (41.6)	
<65	80 (47.8)	47 (58.7)	33 (41.2)	
Time of arrest				< 0.001
Day shifts (08:00-15:59)	79 (42.5)	33 (41.7)	46 (58.2)	
Night shifts (16:00-07:59)	107 (57.5)	76 (71.1)	31(29.9)	
Type of arrest				< 0.05
Cardiac arrest	112 (58.4)	72 (64.2)	40 (35.7)	
Respiratory arrest	44 (17.5)	17 (38.6)	27 (61.3)	
Cardiopulmonary arrest	20 (24.1)	10 (50)	10 (50)	
Etiology				< 0.001
Respiratory	66 (35.5)	31 (46.9)	35 (53.1)	
Cardiac	54 (29.1)	32 (59.2)	22 (40.8)	
Cerebrovascular	31 (16.7)	20 (64.5)	11 (35.5)	
Malignity	19 (10.7)	16 (84.2)	3 (15.8)	
Renal Failure	10 (5.4)	6 (60)	4 (40)	
Other	6 (3.2)	4 (66.6)	2 (33.4)	
Duration of CPR attempt				< 0.001
≤ 15 min	60 (32.3)	5 (8.3)	55 (91.7)	
>15 min	126 (67.7)	104 (82.5)	22 (17.5)	
First monitored Rhythm				< 0.05
VT/VF	17 (9.1)	2 (11.8)	15 (88.2)	
Asystole	94 (50.5)	57 (60.6)	37 (39.4)	
PEA	48 (25.8)	37 (77.1)	11 (22.9)	
Bradycardia	20 (10.8)	9 (45)	11 (55)	
Unknown	7 (3.8)	4 (57.1)	3 (42.9)	
Location of Arrest				< 0.05
Ward	75 (40.3)	38 (50.6)	37 (49.4)	
CCU/ICU	97 (52.2)	64 (65.9)	33 (34.1)	
ED	9 (4.8)	4 (44.4)	5 (55.6)	
Other	5 (2.7)	2 (40)	3 (60)	

ROSC = Rates of return of spontaneous circulation; CPR = cardiopulmonary resuscitation; PEA = pulseless electrical activity; CCU = coronary care unit; ICU = intensive care unit;

DISCUSSION

CA and sudden death arrest ratios decreased among in-hospital patients after establishment of medical emergency teams[2,7,8]. The MERIT study revealed that code blue events were more common in hospitals with a medical emergency team. Such hospitals had significantly lower sudden death and cardiopulmonary arrest ratios[5].

Recent studies have reported ROSC ratios of 45 - 60% and survival to hospital discharge ratios of 17 -18.4%[4,9,10]. In this study, rates of ROSC and survival to hospital discharge were 41.4% and 6.4% respectively. These rates of ROSC and survival to hospital discharge were lower than the rates in countries with developed MET system for a long time. The introduction of MET system in all hospitals and increasing effectiveness could improve ROSC and live discharge ratios from hospitals.

Signs of physiological instability are evident in 80% of CA patients 24 h prior to the emergency[2,11]. MET activation criteria are defined as major changes in vital signs. In this study, the code blue calls were commonly used for cardiopulmonary arrests. This may be a factor that might increase the mortality in those patients. Moreover, in this study, only one patient who did not receive CPR had experienced cardiopulmonary arrest, following medical treatment, subsequently. Therefore, code blue calls may be used more commonly in patients with major changes in vital signs.

Another dilemma for MET system is that the medical staff hesitate to activate the system[7,8,12]. In our hospital, there were no criteria for blue code system activation. A standard, easy code blue activation rule that could be used in all hospitals may help decreasing in-hospital mortality.

Some studies have revealed that age is an important predictor of mortality after CPR[13-15], while some other studies, including the present one, opines that it is not important[16,17].

Rates of ROSC and survival to discharge are affected by the quality of the MET call system and time of arrival to the scene[17,18]. Under the on call system, which was designed fully by us, MET arrived to the scene within 2 min time for 74.7% of total code blue calls. In our opinion, the results indicate that this code blue system has been running well and we suggest that it may be a good option for other hospitals too.

ROSC ratios tend to decrease during night shifts[13,14,19]. We also found similar results. This may

be related to negligence and indifference of MET members and healthcare providers performing code blue calls, and the lack of specialists who are concerned about arrests and CPR, during night shifts. Providing attention and increasing vigilance of all members of night shifts may help to reduce the mortality ratios.

Additionally, studies showed that even in developed countries, many of the mistakes during CPR are caused by avoidable errors made by healthcare providers[20]. A previous study revealed that recurrent ACLS courses increase the level of knowledge in healthcare providers[21]. For this reason, before MET introduction, we trained Basic Life Support, ACLS and blue code call to all healthcare providers and all members of the MET.

In accordance with the results of other studies[13,18,19], ROSC ratio was higher during respiratory arrest and significantly lower during cardiac arrest. Respiratory arrest and upper airway obstructions may be treated prior to CA. Adequate and timely response to respiratory arrest will significantly reduce mortality ratios.

Respiratory and cardiac diseases are common causes of cardiopulmonary arrest[10,17]. We found similar results. Healthcare providers should be aware of this risk and staff should be trained to activate the emergency medical system when indicated by patients' symptoms.

ROSC and survival to hospital discharge ratios are lower in patients with end-stage disease and co-morbid disease, malignancy[15]. In this condition, even though code blue calls are activated on time, the ROSC and survival ratios in hospitalized patients who received CPR might be decreased.

ROSC are higher in the first 15 min and longer CPR times are associated with worse ROSC outcomes[13]. In this study, all the patients having CPR within 15 minutes time, responded well to CPR. Early activation of the code blue system, an early response of the MET and effective CPR may reduce the mortality ratios.

Previous studies have shown that most of the patients with initial VT/VF rhythm responded to CPR[4,10,14] and patients with an initial rhythm of PEA have significantly lower ROSC ratios[13,16]. In the present study, the ROSC ratios in VT/VF patients were significantly higher than in PEA patients. Therefore, critically ill patients should be monitored and the code blue system should be activated in VT/VF rhythms on time.

Limitations

There are some limitations in our study. First, this study is a single-center, nonrandomized, and observational study. Data were reviewed retrospectively from the blue code forms. In particular, this might have lead to the emergence of a shorter duration than real arrival time at the scene. Secondly, until the MET is established, data of patients who received CPR could not be reached in hospital records. Therefore, impact of the MET introduction on the survival from previous data could not have been fully explained. Lastly, we did not have any data to prove effectiveness of regulations that we recommended to be more effective of MET calls.

CONCLUSIONS

Response to CPR attempts is affected by early activation of the code blue system and early response of the MET. In our code blue calls system, MET arrived at the scene in two minutes in many part of calls. MET activation may be used more commonly in critical patients with major changes in vital signs. MET and code blue systems should be set up in all hospitals. Therefore, rates of ROSC and survival to discharge may be increased.

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Original Article

The Number and Awareness of Rhinoplasty and People Preferences of the Shape of Nose

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ABSTRACT

Objectives: To determine the number of Saudi adults who want to undergo rhinoplasty, to assess their level of awareness and to evaluate their nose shape preference
Design: Cross-sectional study. The sample was selected randomly during October 2014
Setting: The city of Riyadh, Saudi Arabia with a cluster sampling of Riyadh malls
Subjects: Five hundred forty-five Saudi adults were included
Intervention: Self-administered questionnaire
Main outcome measure: Number and awareness of rhinoplasty
Results: 73.4% of participants knew what rhinoplasty is. 30% knew the different types of surgical and non-surgical options. 59.3% did not know its complications. 70% had not encountered any information about rhinoplasty from books, brochures. 40.7% expected the success rate for rhinoplasty to between 50% and 70%. 29.5% wanted to preform rhinoplasty themselves. 61.1% think that psychological effects could explain the reasoning behind rhinoplasty. More than 90% desire a straight nose, narrow nostrils and smaller nose size. 58.7% and 82% want the nose tip to be up and sharp, respectively. Nose length preferences were distributed equally among participants.
Conclusions: Most of the participants were not aware of different rhinoplasty options or of rhinoplasty's complications. Most of them thought that the reason behind an increasing number of rhinoplasties is a social and psychological effect.

KEY WORDS: appearance, cosmetic surgery, nose shape, prevalence

INTRODUCTION

Rhinoplasty is a reconstructive plastic surgery, usually done to restore the nasal function after trauma or to enhance the nose's appearance. Incidence of rhinoplasty is presently increasing around the world, especially in the Gulf region. According to the International Association of Plastic Surgery's 2013 statistics of the plastic surgeries performed worldwide, 954,423 rhinoplasty procedures were performed; at 8.2%, it is considered to be the fifth most commonly performed plastic procedure worldwide[1]. Moreover, according to the International Association of Plastic Surgery's 2010 statistics, Saudi Arabia was one of the top 25 countries in the total number of plastic surgeries performed; of the 45,398 procedures, 6,404 were rhinoplasty, making it the second most common plastic surgery in Saudi Arabia[2].

Research Objectives

1. To determine the number of Saudi adults who want to undergo rhinoplasty
2. To evaluate Saudi population awareness of rhinoplasty options and complications
3. To assess the reasons for the increased demand for cosmetic rhinoplasty in Saudi Arabia
4. To determine the desired nose shape among the Saudi population

SUBJECTS AND METHODS

Study design: It is a cross-sectional qualitative study. It was conducted in the city of Riyadh, Saudi Arabia. The samples were recruited randomly during October 2014 and the eligible participants were informed about the study and its purpose.

Study setting: Riyadh is the capital city of and largest city in Saudi Arabia. It is considered one of the modern and highly developed cities in Saudi Arabia, and a home to 5.7 million people, 61 percent of which are Saudi citizens[3].

Population under study: All adults (18-years-old and-older, Saudis) who are visiting Riyadh malls in all city

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districts. Participants who had undergone rhinoplasty in their lives have been excluded.

Data collection methods

The research team conducted data collection during October 2014. Information was gathered through a self-administered questionnaire, consisting of 18 questions. The questionnaire addressed the following elements: demographic features, rhinoplasty awareness, knowledge of different treatment options and complications, the number of participants who desire their own rhinoplasty, the reasons for participants to undergo rhinoplasty and the preferred nose shape post-rhinoplasty (see sample questionnaire in Appendix).

Sample size and sampling technique

Cluster sampling technique was used to divide Riyadh into four clusters, south, north, east and west, and two malls were randomly selected in each cluster. Surveys were disturbed to a total of 545 random eligible participants.

Data analysis plan

The data was descriptively analysed using SPSS statistical program. A level of significance was set at (α) <0.05, with a confidence interval of 95%.

Ethical considerations

Verbal consent was taken from all participants before they answered the questionnaires. The consent form included, the purpose and objectives of the research. No incentive or reward was given to the participants.

RESULTS

Demographic characteristics and frequencies

A total of 545 participants were included, of which 412 (75.6%) were females and 133 (24.4%) were males. As shown in Table 1, most (402) of the included participants were between 18 - 29 years old (73.8%).

With regard to education level, 422 (77.4%) participants were highly educated, with a bachelor's degree or other higher education. More than half of the participants were single: 364 (66.8%), compared to only 172 married participants (31.6%).

Regarding rhinoplasty awareness, most (400) of the participants (73.4%) knew what rhinoplasty is and had some idea about it. In further questioning, only 177 (32.5%) of them knew the different types of surgical options and 168 (30.8%), for the non-surgical options for rhinoplasty. More than half (323; 59.3%) did not know about the complications of rhinoplasty, 384 (70%) had not encountered or read any information about rhinoplasty from books or brochures and 222 (40.7%) expected the success rate for rhinoplasty to be between 50% and 70%. Two hundred ninety-five (54.1%) participants had a relative or a friend who underwent rhinoplasty, and 161 (29.5%) actually wanted their own rhinoplasty. Also, 135 (24.8%) were interested in performing any other type of plastic surgeries.

When participants were asked for their opinion regarding reasons behind undergoing a rhinoplasty, almost half (274; 50.3%) of them disagreed that social effects were the reason, and the other half (271) agreed (49.7%). Three hundred thirty-three (61.1%) of the respondents thought that psychological effects could explain the desire for rhinoplasty. Half of the participants (279; 51.2%) agreed that a broken nose or functional impairment could be a reason for rhinoplasty. Only 214 (39.3%) said the media affects people; moreover, only 170 (31.2%) agreed that the availability and easy accessibility of different surgical and non-surgical options in the country could be the reason. Most participants disagreed that having similar nose shapes among family members explain the reason for undergoing a rhinoplasty.

Most of the participants (511; 93.8%) prefer a straight nose. For the nose tip, some participants prefer an up nose tip (320; 58.7%), and 225 (41.3%) prefer down nose tip. Four hundred ninety-nine (91.6%) participants desired narrow nostrils, and 447 (82%) preferred a sharp nose tip. The ideal nose length was distributed equally among the participants: 274 (50.3%) wanted a long nose, and 271 (49.7%) wanted a short nose. Five hundred seventeen (94.9%) participants preferred a small nose size. Majority of the participants (337; 61.8%) wished to have a less prominent side view of the nose, and 469 (86.1%) wanted a straight nose from the side view of the face.

Gender comparison

When comparing males' and females' knowledge and awareness (Table 2), 76.7% of females said they had an idea about rhinoplasty compared to 63.2% of males, which is a significant difference ($p = 0.002$). Among females, 38.1% knew the different types of non-surgical options for rhinoplasty, with a significance level of $p = 0.000$ compared to males 15.5%. The percentage of females who knew the complications of rhinoplasty was higher than that of males ($p = 0.000$). Similarly, 43.4% of females expected the success rate for rhinoplasty to be 50 - 70% ($p = 0.000$). Females knew more relatives or friends who had undergone rhinoplasty (59.7%) compared to males (36.8%) ($p = 0.000$). Obviously, more females wanted to perform any other type of plastic surgery compared to males ($p = 0.000$). Among females, 95.4% preferred a straight nose ($p = 0.006$), and 64.1% of females compared to 42.1% males preferred a high nose tip ($p = 0.000$) and narrower nostrils (94.9%) ($p = 0.000$). Also, 86.4% of

Table 1: Demographic characteristics of all participants and frequencies in number and percentage

Variables	Frequency N = 545	Percentage
Age (year)		
18 - 29 y	402	73.8
30 - 39 y	63	11.6
40 - 49 y	59	10.8
50 - 59 y	17	3.1
60 y and above	4	.7
Gender		
Male	133	24.4
Female	412	75.6
Marital status		
Single	364	66.8
Married	172	31.6
Widow	1	.2
Divorced	8	1.5
Education		
Low Education	123	22.6
High Education	422	77.4
Do you have any idea about rhinoplasty?		
Yes	400	73.4
No	145	26.6
Do you know about the different types of non-surgical options for rhinoplasty?		
Yes	177	32.5
No	368	67.5
Do you know about the complications of rhinoplasty?		
Yes	222	40.7
No	323	59.3
Do you know about the different types of surgical options for rhinoplasty?		
Yes	168	30.8
No	377	69.2
Did you read any information about rhinoplasty from books or brochures?		
Yes	161	29.5
No	384	70.5
What percentage do you expect for the success of operations rhinoplasty?		
Less than 50 %	76	13.9
50 % to 70 %	222	40.7
70 % to 90 %	176	32.3
More than 90 %	71	13.0
Did anyone of your relatives or friends underwent a rhinoplasty?		
Yes	295	54.1
No	250	45.9
Do you want to do a rhinoplasty?		
Yes	161	29.5
No	384	70.5
What do you think is the reason behind rhinoplasty? (you can pick more than one)		
Social effect	271	49.7
Psychological effect	333	61.1
Broken nose or functional impairment	279	51.2
Media effect	214	39.3
The availability of surgical and non-surgical options of rhinoplasty in your country	170	31.2
Genetic. (Most family member have the same nose shape)	39	7.2
Do you want to do any other type of plastic surgeries?		
Yes	135	24.8
No	410	75.2
What type of nose you prefer?		
Straight nose	511	93.8
Sloped nose	34	6.2
Nose tip		
Up	320	58.7
Down	225	41.3
Nose nostrils		
Narrower	499	91.6
Wider	46	8.4
Nose tip		
Sharp	447	82.0
Wide	98	18.0
The length of the nose		
Longer	274	50.3
Shorter	271	49.7
The size of the nose		
Smallest	517	94.9
Largest	28	5.1
Side view of the nose		
Less prominent	337	61.8
More prominent	208	38.2
Side view of the nose		
Straight	469	86.1
Humped	50	9.2
Sloped	26	4.8

females desired a sharp nose tip compared to males (68.4%) ($p = 0.000$), a longer nose (52.9%) of females and 42.1% of males ($p = 0.030$); 96.6% of females wanted a smaller size nose compared to 89.5% of males ($p = 0.001$). For the side view of the nose, 59.0% of females selected a less prominent nose, and 89.8% selected a straight nose compared to males (70.7% and 74.4%, respectively), with a significance level of $p = 0.016$ and $p = 0.000$, respectively.

Marital status comparison

When comparing married participants with single participants, the single participants were more aware of rhinoplasty (78.3%) with a significant difference of ($p = 0.000$), and 34.9% of them knew the different non-surgical types of rhinoplasty compared to 26.2% of married participants ($p = 0.043$). The single participants were more aware ($p = 0.003$) of the different surgical options. Moreover, 36.0% of married participants had read information about rhinoplasty from books or brochures than the single participants - 26.4% ($p = 0.022$), and more married participants (44.8%) thought that the success rate for rhinoplasty is between 50% and 70% ($p = 0.000$). 32.1% of the single participants wanted rhinoplasty, than the married participants - 23.3% ($p = 0.035$). Regarding preferred nose shape, single and married participants agreed on the same shape with no significant difference, except for the nose tip: 62.4% of singles preferred a high nose tip compared to 50.0% of married participants ($p = 0.007$). Table 3 displays detailed results.

Age comparison

Results were compared between different age groups, which are divided into younger and older age groups, as shown in table 4. Regarding people's knowledge about rhinoplasty, majority of the

respondents (77.6%) in the young age group (18 - 29 y) were positive for their knowledge, with a significance difference of ($p = 0.000$). 67.5% of the young age group did not know about non-surgical types of rhinoplasty compared to 72.7% of the older age group (≥ 30 y) ($p = 0.0122$). Approximately, 60% of both the young

Table 2: Gender comparison for the different questions in the study survey in number and percentage %; n = 84 for males and n = 316 for females, with chi-square results statistical significance of P = <0.05

Variables	Frequency N (%)		Chi-Square P- value
	Male N (%)	Female N (%)	
Do you have any idea about rhinoplasty?			0.002
Yes	84 (63.2)	316 (76.7)	
No	49 (36.8)	96 (23.3)	
Do you know about the different types of non-surgical options for rhinoplasty?			0.000
Yes	20 (15.0)	157 (38.1)	
No	113 (85.0)	255 (61.9)	
Do you know about the complications of rhinoplasty?			0.000
Yes	33 (24.8)	189 (45.9)	
No	100 (75.2)	223 (54.1)	
Do you know about the different types of surgical options for rhinoplasty?			0.084
Yes	33 (24.8)	135 (32.8)	
No	100 (75.2)	277 (67.2)	
Did you read any information about rhinoplasty from books or brochures?			0.111
Yes	32 (24.1)	129 (31.3)	
No	101 (75.9)	283 (68.7)	
What percentage do you expect for the success of operations rhinoplasty?			0.000
Less than 50 %	11 (8.3)	65 (15.8)	
50 % to 70 %	43 (32.3)	179 (43.4)	
70 % to 90 %	43 (32.3)	133 (32.3)	
More than 90 %	36 (27.1)	35 (8.5)	
Did anyone of your relatives or friends underwent a rhinoplasty?			0.000
Yes	49 (36.8)	246 (59.7)	
No	84 (63.2)	166 (40.3)	
Do you want to do a rhinoplasty?			0.070
Yes	31 (23.3)	130 (31.6)	
No	102 (76.7)	282 (68.4)	
Do you want to do any other type of plastic surgeries?			0.000
Yes	17 (12.8)	118 (28.6)	
No	116 (87.2)	294 (71.4)	
What type of nose you prefer?			0.006
Straight nose	118 (88.7)	393 (95.4)	
Sloped nose	15 (11.3)	19 (4.6)	
Nose tip			0.000
Up	56 (42.1)	264 (64.1)	
Down	77 (57.9)	148 (35.9)	
Nose nostrils			0.000
Narrower	108 (81.2)	391 (94.9)	
Wider	25 (18.8)	21 (5.1)	
Nose tip			0.000
Sharp	91 (68.4)	356 (86.4)	
Wide	42 (31.6)	56 (13.6)	
The length of the nose			0.030
Longer	56 (42.1)	218 (52.9)	
Shorter	77 (57.9)	194 (47.1)	
The size of the nose			0.001
Smallest	119 (89.5)	398 (96.6)	
Largest	14 (10.5)	14 (3.4)	
Side view of the nose			0.016
Less prominent	94 (70.7)	243 (59.0)	
More prominent	39 (29.3)	169 (41.0)	
Side view of the nose			0.000
Straight	99 (74.4)	370 (89.8)	
Humped	21 (15.8)	29 (7.0)	
Sloped	13 (9.8)	13 (3.2)	

Table 3: Marital status comparison for the different questions in the study survey in number and percentage for single and married respondents, with chi-square results statistical significance of P = <0.05

Variables	Frequency N (%)		Chi-Square P- value
	Single N (%)	Married N (%)	
Do you have any idea about rhinoplasty?			0.000
Yes	285 (78.3)	110 (64.0)	
No	79 (21.7)	62 (36.0)	
Do you know about the different types of non-surgical options for rhinoplasty?			0.043
Yes	127 (34.9)	45 (26.2)	
No	237 (65.1)	127 (73.8)	
Do you know about the complications of rhinoplasty?			0.493
Yes	151 (41.5)	66 (38.4)	
No	213 (58.5)	106 (61.6)	
Do you know about the different types of surgical options for rhinoplasty?			0.003
Yes	126 (34.6)	38 (22.1)	
No	238 (65.4)	134 (77.9)	
Did you read any information about rhinoplasty from books or brochures?			0.022
Yes	96 (26.4)	62 (36.0)	
No	268 (73.6)	110 (64.0)	
What percentage do you expect for the success of operations rhinoplasty?			0.000
Less than 50 %	36 (9.9)	37 (21.5)	
50 % to 70 %	144 (39.6)	77 (44.8)	
70 % to 90 %	132 (36.3)	39 (22.7)	
More than 90 %	52 (14.3)	19 (11.0)	
Did anyone of your relatives or friends underwent a rhinoplasty?			0.065
Yes	187 (51.4)	103 (59.9)	
No	177 (48.6)	69 (40.1)	
Do you want to do a rhinoplasty?			0.035
Yes	117 (32.1)	40 (23.3)	
No	247 (67.9)	132 (76.7)	
Do you want to do any other type of plastic surgeries?			0.832
Yes	90 (24.7)	41 (23.8)	
No	274 (75.3)	131 (76.2)	
What type of nose you prefer?			0.077
Straight nose	337 (92.6)	166 (96.5)	
Sloped nose	27 (7.4)	6 (3.5)	
Nose tip			0.007
Up	227 (62.4)	86 (50.0)	
Down	137 (37.6)	86 (50.0)	
Nose nostrils			0.526
Narrower	336 (92.3)	156 (90.7)	
Wider	28 (7.7)	16 (9.3)	
Nose tip			0.597
Sharp	301 (82.7)	139 (80.8)	
Wide	63 (17.3)	33 (19.2)	
The length of the nose			0.267
Longer	176 (48.4)	92 (53.5)	
Shorter	188 (51.6)	80 (46.5)	
The size of the nose			0.115
Smallest	350 (96.2)	160 (93.0)	
Largest	14 (3.8)	12 (7.0)	
Side view of the nose			0.828
Less prominent	225 (61.8)	108 (62.8)	
More prominent	139 (38.2)	64 (37.2)	
Side view of the nose			0.214
Straight	317 (87.1)	144 (83.7)	
Humped	28 (7.7)	21 (12.2)	
Sloped	19 (5.2)	7 (4.1)	

Table 4: Age comparison for the different questions in the study survey in number and percentage of age 18-29 y and age 30 y and above, with chi-square results statistical significance of P = <0.05

Questions in the Study	Frequency N (%)		Chi-Square P- value
	18 - 29 y N (%)	> 30 y N (%)	
Do you have any idea about rhinoplasty?			
Yes	312 (77.6)	88 (61.5)	0.000
No	90 (22.4)	55 (38.5)	
Do you know about the different types of non-surgical options for rhinoplasty?			0.122
Yes	138 (34.3)	39 (27.3)	
No	264 (65.7)	104 (72.7)	
Do you know about the complications of rhinoplasty?			0.729
Yes	162 (40.3)	60 (42.0)	
No	240 (59.7)	83 (58.0)	
Do you know about the different types of surgical options for rhinoplasty?			0.034
Yes	134 (33.3)	34 (23.8)	
No	268 (66.7)	109 (76.2)	
Did you read any information about rhinoplasty from books or brochures?			0.037
Yes	109 (27.1)	52 (36.4)	
No	293 (72.9)	91 (63.6)	
What percentage do you expect for the success of operations rhinoplasty?			0.000
Less than 50 %	41 (10.2)	35 (24.5)	
50 % to 70 %	157 (39.1)	65 (45.5)	
70 % to 90 %	145 (36.1)	31 (21.7)	
More than 90 %	59 (14.7)	12 (8.4)	
Did anyone of your relatives or friends underwent a rhinoplasty?			0.907
Yes	217 (54.0)	78 (54.5)	
No	185 (46.0)	65 (45.5)	
Do you want to do a rhinoplasty?			0.005
Yes	132 (32.8)	29 (20.3)	
No	270 (67.2)	114 (79.7)	
Do you want to do any other type of plastic surgeries?			0.585
Yes	102 (25.4)	33 (23.1)	
No	300 (74.6)	110 (76.9)	
What type of nose you prefer?			0.439
Straight nose	375 (93.3)	136 (95.1)	
Sloped nose	27 (6.7)	7 (4.9)	
Nose tip			0.000
Up	255 (63.4)	65 (45.5)	
Down	147 (36.6)	78 (54.5)	
Nose nostrils			0.169
Narrower	372 (92.5)	127 (88.8)	
Wider	30 (7.5)	16 (11.2)	
Nose tip			0.942
Sharp	330 (82.1)	117 (81.8)	
Wide	72 (17.9)	26 (18.2)	
The length of the nose			0.234
Longer	196 (48.8)	78 (54.5)	
Shorter	206 (51.2)	65 (45.5)	
The size of the nose			0.242
Smallest	384 (95.5)	133 (93.0)	
Largest	18 (4.5)	10 (7.0)	
Side view of the nose			0.375
Less prominent	253 (62.9)	84 (58.7)	
More prominent	149 (37.1)	59 (41.3)	
Side view of the nose			0.136
Straight	351 (87.3)	118 (82.5)	
Humped	31 (7.7)	19 (13.3)	
Sloped	20 (5.0)	6 (4.2)	

and old age groups did not know about complications of rhinoplasty; 33% of the young age group knew about the complications of rhinoplasty, while only 23% of the older age group knew about it ($p = 0.729$). 66.7% of the young age group knew about different surgical options, compared to 76.2% of the old age group with a significance difference of ($p = 0.0034$). 36.4% from the older age group received information from books and brochures, compared to 27% of the younger age group ($p = 0.037$). When asked about the success rate of this procedure, 39.1% of the younger age group thought it was between 50 - 70% against 45.5% of the older age group ($p = 0.000$). While 32.8% of the younger age group wanted a rhinoplasty, 79.7% of the older age group did not want to do it ($p = 0.005$).

93.8% of both the age groups preferred a straight nose. 63.4% of the younger age group preferred the nose tip to be up and 45.5% of the older age group preferred the same ($p = 0.000$). Regarding the nostrils, majority of both age groups (91.6%) preferred it to be narrower, and 82% of both groups wanted their nose tip to be sharp. Almost 50% of both age groups wanted a longer nose. Most participants (94.9%) of both the age groups wanted a smaller nose size. 61.8% of both age groups wanted their side view of the nose to be less prominent, and 86.1% wanted it to be straight.

Education comparison

A comparison between participants' education (low education and high education) is presented in table 5. 73.4% of both groups said they knew about rhinoplasty. 67.5% of both education groups did not know about the different types of non-surgical options for rhinoplasty, 59.3% of both the education groups did not know about any complications and 69.2% of both education groups did not know about surgical options for rhinoplasty. On the other hand, 70.5% of both the groups had not read any information from books or brochures, with no statistical significance difference between the groups.

When asked about the success of rhinoplasty, most of the respondents from both education groups thought it was between 50 - 70% success rate: 48.0% of low education participants and 38.6% of high education participants, with a significance difference of ($P = 0.028$). 54.1% of both groups knew a relative or friend who had undergone rhinoplasty. 70.5% of both education groups did not want a rhinoplasty themselves, and 75.2% of them did not want any other type of plastic surgery.

Regarding preference, 93.8% of both the age groups preferred a straight nose, 58.7% of them preferred a high nose tip, 91.6% preferred narrow nostrils and 82.0% prefer a sharp nose tip. Half of both groups preferred a long nose, and 94.9% of both

Table 5: Education comparison for the different questions in the study survey in number and percentage for high and low education, with chi-square results statistical significance of p = <0.05

Questions in the Study	Frequency N (%)		Chi-Square P- value
	Low Education N (%)	High Education N (%)	
Do you have any idea about rhinoplasty?			0.767
Yes	89 (72.4)	311 (73.7)	
No	34 (27.6)	111 (26.3)	
Do you know about the different types of non-surgical options for rhinoplasty?			0.375
Yes	44 (35.8)	133(31.5)	
No	79 (64.2)	289 (68.5)	
Do you know about the complications of rhinoplasty?			0.139
Yes	43 (35.0)	179 (42.4)	
No	80 (65.0)	243 (57.6)	
Do you know about the different types of surgical options for rhinoplasty?			0.810
Yes	39 (31.7)	129 (30.6)	
No	84 (68.3)	293 (69.4)	
Did you read any information about rhinoplasty from books or brochures?			0.550
Yes	39 (31.7)	122 (28.9)	
No	84 (68.3)	300 (71.1)	
What percentage do you expect for the success of operations rhinoplasty?			0.028
Less than 50 %	21 (17.1)	55 (13.0)	
50 % to 70 %	59 (48.0)	163 (38.6)	
70 % to 90 %	35 (28.5)	141 (33.4)	
More than 90 %	8 (6.5)	63 (14.9)	
Did anyone of your relatives or friends underwent a rhinoplasty?			0.265
Yes	72 (58.5)	223 (52.8)	
No	51 (41.5)	199 (47.2)	
Do you want to do a rhinoplasty?			0.134
Yes	43 (35.0)	118 (28.0)	
No	80 (65.0)	304 (72.0)	
Do you want to do any other type of plastic surgeries?			0.006
Yes	42 (34.1)	93 (22.0)	
No	81 (65.9)	329 (78.0)	
What type of nose you prefer?			0.159
Straight nose	112 (91.1)	399 (94.5)	
Sloped nose	11 (8.9)	23 (5.5)	
Nose tip			0.087
Up	64 (52.0)	256 (60.7)	
Down	59 (48.0)	166 (39.3)	
Nose nostrils			0.334
Narrower	110 (89.4)	389 (92.2)	
Wider	13 (10.6)	33 (7.8)	
Nose tip			0.066
Sharp	94 (76.4)	353 (83.6)	
Wide	29 (23.6)	69 (16.4)	
The length of the nose			0.231
Longer	56 (45.5)	218 (51.7)	
Shorter	67 (54.5)	204 (48.3)	
The size of the nose			0.088
Smallest	113 (91.9)	404 (95.7)	
Largest	10 (8.1)	18 (4.3)	
Side view of the nose			0.682
Less prominent	78 (63.4)	259 (61.4)	
More prominent	45 (36.6)	163 (38.6)	
Side view of the nose			0.322
Straight	103 (83.7)	366 (86.7)	
Humped	11 (8.9)	39 (9.2)	
Sloped	9 (7.3)	17 (4.0)	

education groups' participants wanted a small size nose. Regarding the side view of the nose, 61.8% of both groups wanted it more prominent, and 86.1% of both education groups wanted a straight side view of the nose.

DISCUSSION

Due to the increasing number of plastic surgeries, and rhinoplasty in particular, the present study attempts to determine the number of Saudi adults who desire rhinoplasty; their level of awareness regarding rhinoplasty options, complications and the justifications behind rhinoplasty; and most importantly, what nose shape people desire. Results indicated that most of the participants thought they had an idea about rhinoplasty, but when questioned further, only a few of them knew different surgical and non-surgical options for rhinoplasty or are aware of the complications of rhinoplasty. The results showed that a large portion of participants had not read about rhinoplasty in books or brochures; this lack of awareness may be attributed to the lack of information provided to the targeted community members through different means like books, magazines and radio or television programs by the specialized health care providers.

Also, results showed that 29.5% of participants actually wanted a rhinoplasty, which is a high percentage from randomly selected participants compared to other studies in the literature; also 24.8% of our participants are willing to undergo other types of plastic surgeries. A study conducted in Iran in 2012 of 320 female students found that more than half of the respondents wanted to have their noses done for cosmetic reasons only. More than half of those students did not know about the complications[4]. In our study, there was a significant difference between male and female respondents when they were asked about their chances of having rhinoplasty or any other type of plastic surgery. This is, perhaps, not unanticipated, given the superior sociocultural burden on women to achieve ideals of physical attractiveness.

Results showed that more than half of participants knew a friend or a relative who had a rhinoplasty; knowing someone close and seeing their results post-rhinoplasty can greatly influence one's decision to have their own rhinoplasty. A 2005 study of female undergraduates by Delinsky addresses the personal and vicarious experience and the likelihood of undergoing cosmetic surgery. A key finding in Delinsky's study was that the greater the vicarious experience of friends and family who had undergone cosmetic surgery, greater is the likelihood of participants undergoing their own cosmetic surgery in the future[5].

In our study, participants believed that social and psychological effects and functional disability were the most common reasons to undergo rhinoplasty. Also, almost 40% of participants thought that media effects increased the likelihood of undergoing rhinoplasty, in contrast to a study by Brown published in 2007, which found that media exposure did not significantly predict any likelihood of undergoing cosmetic procedures[6].

In our study, we found the ideal nose shape desired by Saudi participants was a straight nose with high profile, sharp tip and narrow nostrils, and a small nose with a straight and less prominent side view. With regard to nose length, the participants equally preferred short and long noses. In comparison to a study done of a Korean population, the preferred nose shape was of nasal height 6 mm, straight shape of the dorsum, 35 degree nasofacial angle, 105 degree tip angle, straight axis of the alar, smooth concave and straight shape of the columella limb and the smooth, concave shape of the subnasal segment[7]. In a 2014 study, Iranian patients were satisfied with a natural nose, decreased nose projection and an elevated low-profile tip[8].

When classifying the participants according to age, the younger population was more aware of rhinoplasty than the older age group, including different types of surgical and non-surgical rhinoplasty as well as the complications involved. This difference could be due to the fact that the younger age group is more concerned about their appearance and look; so they have read about it more than the older generation.

Regarding the shape of the nose, both the age groups wanted a smaller nose size, less prominent on the side view and straighter. Both the less and highly educated were found to be equally aware about rhinoplasty, different surgical and non-surgical options, related complications and the success rate.

CONCLUSION

In conclusion, most of the participants were found to be not aware of the varying types of surgical and non-surgical options of rhinoplasty and of the potential complications involved in it. With regard to the purpose of undergoing rhinoplasty, participants thought that social and psychological effects were the reason behind the increase in such surgeries. Also, friends' and relatives' influence was a major motive, since most of the participants knew someone who had undergone a rhinoplasty. A good number of participants wanted to undergo rhinoplasty or other type of plastic surgery. Regarding the shape of the nose, most of the participants favoured a straight, high and sharp nose tip with narrow nostrils and small in size with a less prominent and straight side view of the face.

Recommendations

As the number of rhinoplasty surgeries continues to increase, we recommend further research regarding the causes of this increase. We also recommend doing more campaigns to increase awareness of rhinoplasty. Since most of the participants (61%) in our study suggested that the reason behind rhinoplasty is psychological, we suggest rhinoplasty clinics implement psychological evaluation and psychotherapy programs to assess such patients.

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Case Report

Successful Treatment of Disseminated Invasive Aspergillosis with Itraconazole in a Severe Chronic Hepatitis B Patient

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ABSTRACT

Invasive aspergillosis is a rapid, progressive, and often fatal disease that usually affects immunocompromised patients. Opportunistic invasive fungal infections can occur in patients with severe diseases, such as severe hepatic disease although they are immunocompetent. We report a successful case of treatment with itraconazole for a 31-year-old patient with severe chronic hepatitis B (CHB) complicated with disseminated aspergillosis that rapidly progressed to affect his respiratory and central nervous systems as well as the eye. We discussed our experience and recognized that invasive aspergillosis should be considered in severe CHB patients who develop acute respiratory failure or uncontrollable pulmonary infection.

KEY WORDS: antifungal therapy, hepatic failure, immunosuppression, pulmonary infection, tissue transplant

INTRODUCTION

Invasive aspergillosis is a serious complication of solid tissue transplant and cancer patients. Invasive pulmonary aspergillosis has been described in patients with immunocompetence or immunosuppression, such as patients with diabetic mellitus[1], chronic obstructive pulmonary disease (COPD)[2] and chronic liver disease[3]. Without adequate therapy, invasive pulmonary aspergillosis can be complicated by dissemination to the central nervous system (CNS) or by extension to other intra-thoracic structures, including the heart. Recent studies have shown that invasive pulmonary aspergillosis can also occur in patients with acute hepatic failure associated with malignancy or prolonged treatment with antibiotics and steroids[4, 5]. However, there is no report about the case of invasive systemic aspergillosis in patients with hepatic failure.

Voriconazole has been recommended for the treatment of invasive aspergillosis; however, it can cause mucormycosis[6, 7]. Liposomal amphotericin B, caspofungin, and itraconazole have been used as alterative medicines. Here, we report a successful case of treatment with itraconazole in a severe CHB patient with rapidly progressive systemic aspergillosis that affected his respiration, CNS and eye. We recognized that the importance of early diagnosis of invasive aspergillosis and treatment with anti-fungal medicines to support the survival of the patient. We, here, discuss briefly our experience.

CASE REPORT

A 31-year-old Chinese man with a 7-year history of hepatitis B presented with general fatigue, appetite loss and jaundice for 14 days. His hepatic function had been abnormal for more than seven years and he had been treated with medicines intermittently. He was a blue-collar worker and had no history of blood transfusion or drug abuse.

He visited a local hospital for his 3 days of jaundice, general fatigue and fever, and was admitted to the hospital with a diagnosis of severe CHB, billiard tract infection and spontaneous peritonitis. He was treated with commonly used antibiotics, plasma transfusion and oral prednisolone (30 mg/per day). Although his fever was controlled, his jaundice worsened. Ten days after hospitalization, he was transferred to our hospital.

On admission, his body temperature was 36.5 °C, and physical examination revealed severe icterus and abdomen shifting dullness. Laboratory tests indicated that he had abnormal hepatic function (Table 1), and

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Table1: Summary of patient's hepatic function and WBC tests during the course of illness

Hepatic function and WBC	Day 1	Day 22	Day 32	Day 50	Day 103
Total bilirubin (3 - 22 umol/L)	609	789	969	504	66.2
Direct bilirubin (0 - 6 umol/L)	382	447	597	302	37
ALT (5 - 40 u/L)	117	53	70	60	53
AST (8 - 45 u/L)	121	93	61	55	70
Albumin (30 - 50g/L)	28.2	29.6	29.5	30.5	32
PT (9 - 15 s)	23.3	16.5	19.7	16.4	14.1
Temperature (℃)	36.8	36.6	39.2	36.7	36.7
WBC (4 - 10 × 10^9/L)	7.7	7.6	19.9	9.7	5.6

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase , PT = Platelet, WBC = White blood cell

was positive for the HBV-DNA test (4.5 × 10^5 copies/mL), suggesting active hepatitis B. His liver displayed diffuse hepatic parenchymal disease, massive ascites, and bilateral small pleural effusions, determined by ultrasound examination. Diagnostic abdominal puncture collected 800 mL of ascitics that contained a total leukocyte count of 296 × 10^6 cells/L with 10% being neutrophils. He was diagnosed with severe CHB.

The patient was treated intravenously with piperacillin sodium/sulbactam sodium for the control of infection, with lamivudine for hepatitis B infection and artificial liver support-plasma exchange to improve hepatic function. On day 10 post admission, the patient still displayed severe jaundice and he was injected with dexamethasone (10 mg/per day) for 10 days at acupoint zusanli for attempting to relieve jaundice. On day 22, the volume of ascites and pleural effusion was obviously reduced. However, his jaundice became more severe (Table 1). On day 32, the patient developed a high fever (39.2 °C) and abdominal pain, accompanied by a rapid increase in the volume of ascites. His total leukocyte count in ascetics was 580 × 10^6 cells/L with 76% being neutrophils, and his total blood WBC count was 19.9 × 10^9 cells/L with 91% being neutrophils and his liver function worsened (Table 1). Apparently, his infection was not controlled and he was treated with tazocin, but he remained febrile for another three days.

On day 36, he complained of cough with yellow sputum, hemoptysis, dyspnea and visual field defect in his right eye. His sputum culture indicated *Escherichia coli*c (β-lactamase positive), and he was alternatively treated with meropenem. On day 38, a chest CT scan showed multiple pulmonary nodules with a halo sign, and patchy consolidation throughout both lungs (Fig 1). On day 39, the patient was still febrile, and his deficient right visual field was enlarged and was diagnosed with infectious uveitis by an ophthalmologist. Interestingly, his sputum smear showed fungal spores and hyaline

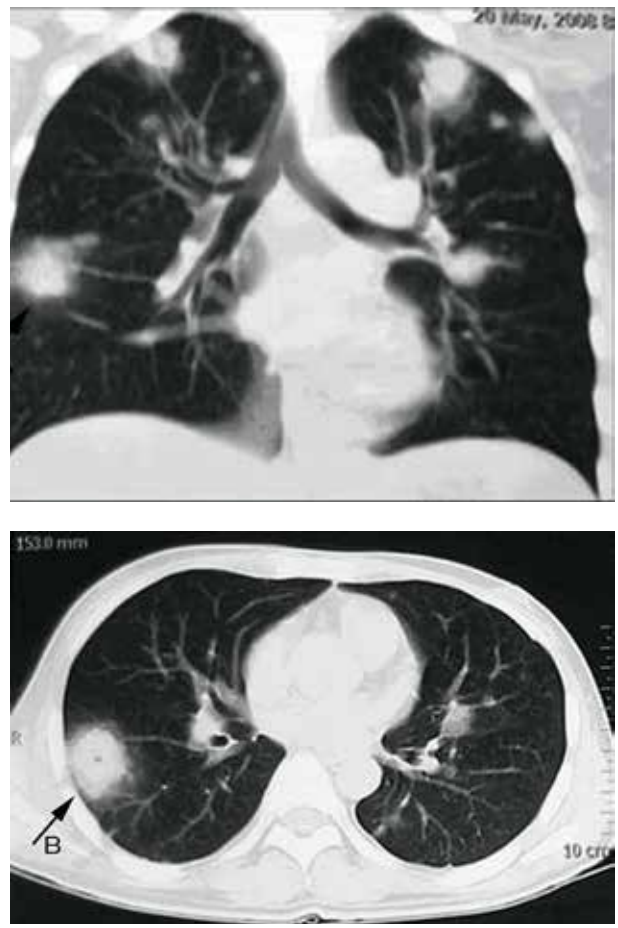


Fig. 1A, B: CT scan of the chest shows multiple pulmonary nodules with a halo sign in the lungs on day 38 post hospitalization. Arrows indicate the lesions.

branching hyphae, and his sputum culture revealed aspergillus species on three occasions (Fig 2). Accordingly, he was diagnosed as disseminated invasive aspergillosis. On day 40, the patient was treated intravenously with L-AMB for one day, but he was intolerant due to a rapid drop in total WBC counts and body temperature. He was then changed to oral itraconazole (200 mg, twice per day) on day 43.

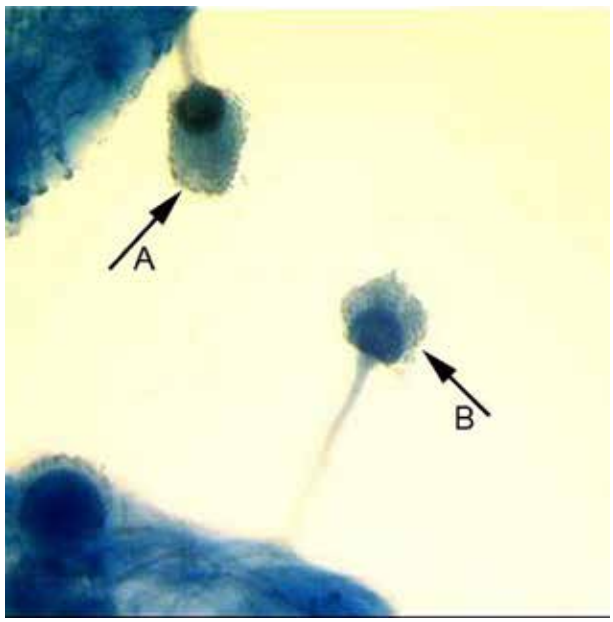
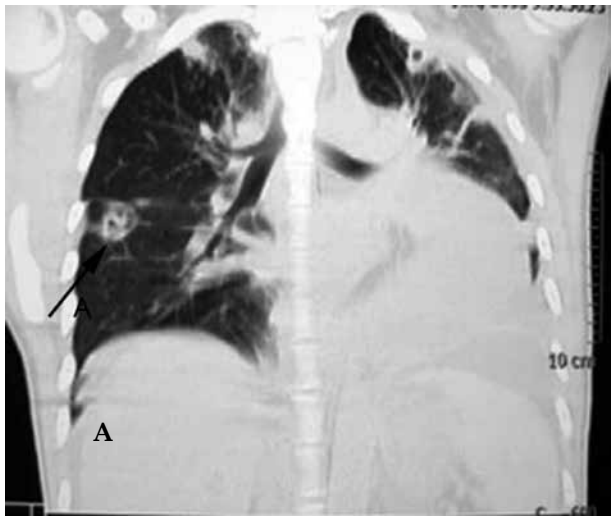


Fig 2: Detection of aspergillus (arrows) in sputum culture on day 39.



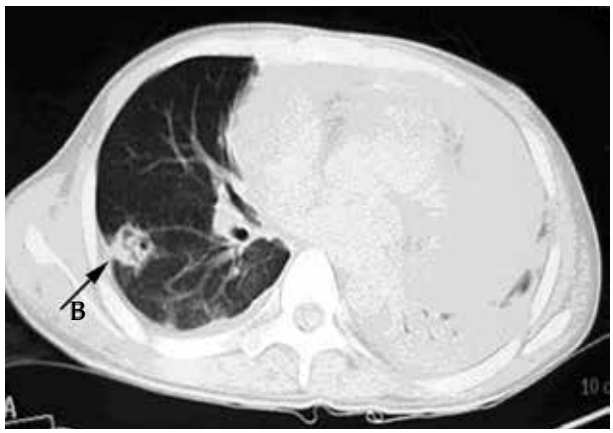


Fig 3A, B: CT scan of the chest shows masses with the halo sign and air-crescent in the right lobe. Arrows indicate the lesions.

On day 48, although the patient's body temperature became normal, he presented neurological symptoms of altered mental status, lethargy, incontinence, left lower limb paralysis and weak right limb muscles. Besides oral itraconazole, he was administered intravenously with mannitol (125 ml, three times per day) for ten days and his overall condition and conscious levels were improved. However, his right eye was blinded. On day 64, a repeat CT scan of the chest showed masses with the halo sign and air-crescent in the right lobe, massive pericardial effusion and small bilateral pleural effusions (Fig 3). A total of 1490 ml of bloody exudates were collected from pericardial drainage. Microbiological examination of pleural and pericardial effusion was negative. On day 73, a CT scan of the brain showed multiple low-density shadows in the bilateral cerebral hemispheres, speculating infection (Fig 4). Cerebrospinal fluid culture reported negative for common pathogens and his cerebrospinal fluid pressure was 50 cm H_2O. Thereafter, the patient felt improved, without cough, phlegem, dyspnea and fever. On day 86, the strength of his left limb muscles recovered to normal. On day 103, another chest CT scan showed that the size of the lesions was minimized (Fig 5). The lesions in the right and left upper zone were completely resolved, and his pericardial effusion was absorbed. On day 111, he was discharged from the hospital.

He was discontinued with oral itraconazole by himself after being discharged from hospital due to an economic reason. Two months later, a repeated CT scan showed persistent scaring and cystic changes in

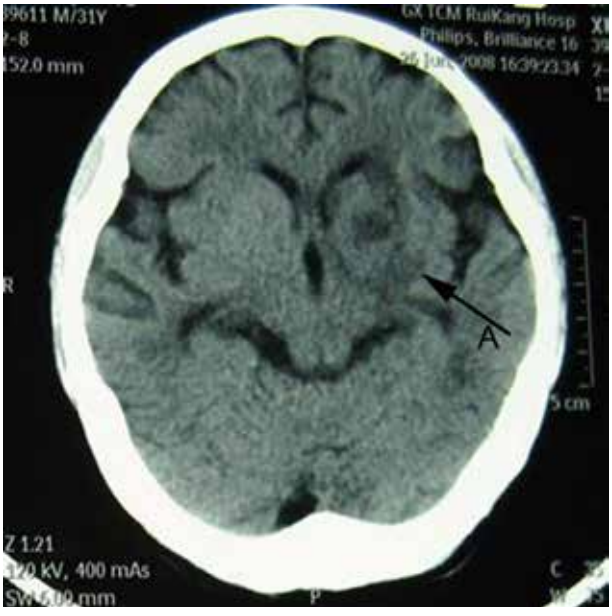


Fig 4: CT scan of the brain shows multiple low-density shadows (arrow) in bilateral cerebral hemispheres, a suspect of infection on day 73.

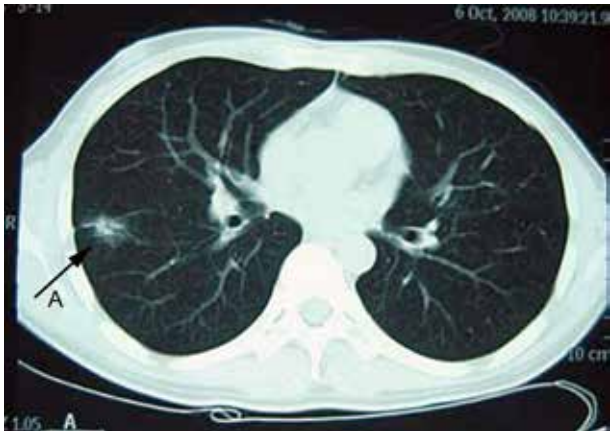


Fig 5: CT scan of the chest shows the reduced size of the lesions, scaring and cystic changes in left and right lower zone 2 months after being discharged from hospital (arrow).

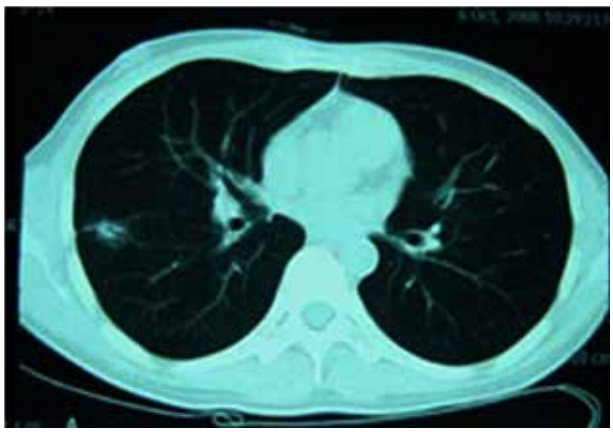


Fig 6: A repeated CT scan 2 months later showed persistent scaring and cystic changes in the left and right lower zone of his lung

the left and right lower zone of his lung (Fig 6) and his right eye remained blind.

DISCUSSION

Aspergillus is a common saprophyte and often found in soil, dust, water, and decaying organisms. Aspergillus species-caused invasive diseases usually affect the lower respiratory tract, sinuses, and skin. Invasive aspergillosis can also extend to the CNS, cardiovascular system, and other tissues by hematogenous dissemination or invading from the contiguous lesions. To the best of our knowledge, this is the first report of successful treatment with itraconazole in a Chinese case with severe CHB and disseminated aspergillosis of multiple organs**.**

The diagnosis of invasive aspergillosis is often difficult and requires histopathological evidence and a positive result of a specimen culture from a normally sterile site[8]. In our case, his sputum showed hyphae and sputum cultures were repeatedly positive for the aspergillus species. However, detection of aspergillus in sputum culture may be unnecessary because these organisms are ubiquitous in the environment and can contaminate airway secretants. When patients have severe diseases and a coagulation deficit, it was impractical to obtain a lung biopsy to confirm invasive aspergillosis. Instead, recent treatment with corticosteroids or with long-term broad-spectrum antibiotics and the clinical features of the halo sign and air-crescent sign on his CT scan, as well as the efficacy of anti-fungal treatment, strongly supported the diagnosis of invasive aspergillosis. Based on the diagnosis of invasive pulmonary aspergillosis, the presence of the compatible clinical symptoms and radiological findings, we speculated that the pulmonary aspergillosis in the patient invaded the pericardium, and spread to the CNS and the eye by hematogenous dissemination.

Patients with hepatic failure have abnormalities in both cell-mediated and humoral immunity, and are susceptible to fugal infections[9,10]. Emerging evidence has also suggested that the liver cirrhosis may be a host-susceptible factor for invasive aspergillosis[4]. Although the patient did not show severe liver fibrosis, he had been treated with long-term broad spectrum antibiotics and with a high dose of corticosteroid, which may contribute to his appearance of invasive aspergillosis. Because treatment with long-term broad spectrum antibiotics can result in the disorder of host microbial balance, reducing their inhibitory effect on fugal infection and with a corticosteroid can inhibit the function of immunocompetent cells, such as macrophages, neutrophils and T-lymphocytes, which are the most important defense in the host against aspergillus infection[11,12]. These, together with his severity of liver disease and high sensitivity to corticosteroid-induced immunosuppresion, made him especially susceptible to aspergillus infection and the development of invasive aspergillosis[13]. Given that he began to develop invasive aspergillosis-related symptoms after hospitalization, it is possible that he acquired aspergillus infection in the hospital. Therefore, we should carefully choose antibiotics for the treatment of infectious diseases in patients with severe liver disease, particularly when combined with corticosteroids in order to prevent potential aspergillus and other fungi infection in hospitalized patients.

Dissemination of aspergillus to the CNS is a devastating complication of invasive aspergillosis because of its high mortality, even if promptly diagnosed and treated[14]. A previous study had demonstrated that the efficacy of treatment of invasive pulmonary aspergillosis with voriconazole

was superior to that with amphotericin B deoxycholate (d-AmB)[15]. Recently, voriconazole has been recommended as the primary medicine for the treatment of invasive pulmonary aspergillosis with Liposomal amphotericin B (L-AmB), caspofungin, and itraconazole as alterative primary medicines. Conceivably, voriconazole should be also applicable to other forms of invasive aspergillosis[14]. However, voriconazole is very expensive and can cause mucormycosis[6,7]. Because the patient could not afford voriconazole and was intolerant to L-AmB, he was treated with itraconazole. Two days after treatment, his clinical conditions were improved and one month later, he became stable. Two months after treatment, his lung lesions were dramatically reduced in a repeat chest CT scan. After discontinuing the treatment for two months, the patient's neurological symptoms almost completely disappeared and he was able to work as previously. Our data indicated that treatment with itraconazole, together with other supportive therapies, was able to control invasive aspergillosis in the patient with severe liver disease. Our findings are consistent with previous observations that solo itraconazole antifungal therapy can effectively control invasive aspergillosis in patients who are refractory to, or intolerant of d-AMB[16, 17].

The duration of therapy for invasive aspergillosis is controversial, but treatment with antifungal agents has been suggested for a minimum of 6 - 12 weeks[14]. We treated the patient with invasive aspergillosis in multiple organs with itraconazole for two months and we not only completely controlled the infection, but also prevented the potential relapse during the 12-month follow-up period. Our experience suggests that it may be unnecessary for antifungal therapy by combining multiple drugs, although previous studies have shown some beneficial effect of the combinational therapy[18,19]. However, the potential deleterious effect of combined antifungal drugs may cause unwelcomed consequences[20].

CONCLUSION

In summary, our experience suggests that physicians should recognize potential invasive aspergillosis when facing a patient with liver failure and uncontrollable pulmonary infection. The patient's historical treatment with long-term broad spectrum antibiotics and recent high dose of corticosteroid can result in his high susceptibility to aspergillus infection. A CT scan, and microbiological examinations, should be considered for the early diagnosis of invasive aspergillosis. If voriconazole is unfeasible, itraconazole can be used for successful treatment of disseminated invasive aspergillus.

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Conflict of interest: All authors declare no conflict of interest in the publication of this case report.

Participation: The first two authors declare equal participation towards this manuscript

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Case Report

P450c17 Deficiency in Kuwaiti Patients

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ABSTRACT

Cytochrome P450c17 deficiency is a very rare autosomal recessive form of congenital adrenal hyperplasia caused by CYP 17A1 gene mutation. We report two phenotypic female patients (46, XY) from Kuwait which are characterized by primary amenorrhea and sexual infantilism with low cortisol, sex and gonadal peptide hormones (inhibin B and AMH). The elder one had high blood pressure and hypokalemia. The multiplex ligation-dependent probe amplification – method of this patient revealed a deletion of exon 1 - 6 in the CYP 17A1 gene.

KEY WORDS: congenital adrenal hyperplasia, disorders of sex development, steroid 17-alpha- hydroxylase, CYP 17A1 gene mutation

INTRODUCTION

Cytochrom P450c17 (EC 1.14.99.9) is a microsomal enzyme, which is necessary for the synthesis of glucocorticoids (17∝-hydroxylase activity) and sex hormones (17, 20-lyase)[1, 2]. A deficiency of this enzyme is a very rare form of congenital adrenal hyperplasia. A prevalence of 1: 50,000 individuals has been reported[3].

The CYP17A1 gene encodes P450c17 and is expressed in the human adrenals and gonads. The lack of CYP 17A1 activity results in an increased secretion of steroids proximal to the deficient enzyme. The enzyme deficiency promotes overproduction of progesterone and of 17∝- deoxysteroids: 11-deoxycorticosterone (DOC) and corticosterone, which displays mineralocorticoid properties that cause hypertension and hypokalemia. Another key feature is the impaired production of gonadal and adrenal steroids. This leads to hypergonadotropic hypogonadism with low sex hormones and to low or even not measurable cortisol secretion.

We examined two patients with complete lack of masculinization, female external genitalia and no uterus. The older one had hypertension and hypokalemia.

CASE REPORT

The patients are siblings born by consanguineous parents (first-degree cousins). They were raised as girls and at the age of 15 and 22 years they were presented to the physician because of primary amenorrhea and lack of pubertal development. They had prepubertal female external genitalia but no uterus. The external genitalia were of female appearance with a blind ending vagina. The karyotype was 46, XY. The younger patient had a normal blood pressure (110/60 mm Hg) and normal serum potassium (4.5 mmol/l). The elder had a hypertension (140/95 mm Hg) and hypokalemia (3.13 mmol/l).

Clinical characteristics of the patients are summarised in Table 1 and plasma basal hormone concentrations in Table 2. It shows the typical pattern of accumulated DOC, corticosterone and progesterone as well as decreased synthesis of 17OH-progesterone, DHEAS, cortisol, testosterone and estradiol. The increased gonadotropins were typical for the primary gonadal failure. The subnormal inhibin B levels in both patients were however, striking. Anti-Mullerian Hormone (AMH) was in the normal range for healthy men, but subnormal for prepubertal patients.

In the pelvic Magnetic Resonance Imaging (MRI) uterus and gonads were not detectable. The multiplex ligation-dependent probe amplification (MLPA) method of the elder patient shows a deletion of exon 1 - 6 in the CYP 17A1 gene.

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Table 1: Clinical characteristics of the patients with P450c17 deficiency

Patient characteristics	Patient 1	Patient 2
Age (yr)	22	15
Karyotype	46, XY	46, XY
External genitalia	female	female
Height (cm)	176	159
Weight (kg)	140	50
BMI (kg/m2)	45	20
BP (mmHg)	140/95	110/60
MRI	no uterus	no uterus

BMI = body mass index; BP = blood pressure; MRI = magnetic resonance imaging

Table 2: Hormone and electrolyte concentrations in the patients with P450c17 deficiency.

Hormones and electrolytes	Patient 1	Patient 2	Normal values
K (mmol/l)	3.1	4.5	3.5 - 5.3
Na (mmol/l)	143	138	135 - 153
Serum Cortisol (ng/ml)	6.5	n.d.	60 - 190
Urine Cortisol (µg/24 h)	14.5	5.6	14 - 75
Progesterone (ng/ml)	4.42	4.86	< 0.1 - 0.3
17OH-Progesterone (ng/ml)	0.06	0.07	0.2 - 1.8
DHEAS (µg/dl)	23	—	238 - 539 (20 - 24 yr)
	—	21	45 - 385 (15 - 19 yr)
11-Desoxycortisol (ng/ml)	< 0.01	< 0.01	< 0.05
11-Desoxycorticosterone (µg/l)	1.42	3.12	0.02 - 0.34
Corticosterone (µg/l)	27	29	1 - 20
Estradiol (pg/ml)	< 5	5	< 45
Free Testosterone	n.d.	< 0.5	4 - 26
LH (IU/l)	39	28	2 - 9
FSH (IU/l)	60	87	1 - 11
Inhibin (pg/ml)	10	2	60 - 300
AMH (ng/ml)	5.2	2.8	1.5 - 4.3 (adult) 10 - 130 (prepubertal)

DHEAS = dehydroepiandrosterone; AMH = Anti-Mullerian Hormone; n.d. = not done

DISCUSSION

In the literature, there are several reports on P450c17 deficiency in congenital adrenal hyperplasia from America, Asia and Europe[1,2,4,5]. Here, we report for the first time, two patients with CYP 17A1 mutation in an Arab country. The parents are cousins. The patients showed the typical signs of this defect. The MLPA revealed a severe exon deletion in the CYP 17A1 gene.

Although cortisol secretion was decreased, the patient had no symptoms of hypocortisolism. Since the corticosterone was increased, which has glucocorticoid effects, it may thus have compensated the hypocortisolism.

The older patient was obese (BMI: 45 kg/m^2), but obesity is apparently not due to the enzyme deficiency, since overweight is endemic in Kuwait and the younger sister has normal weight (BMI: 20 kg/m^2). In addition, the elder had hypertension and hypokalemia, the younger one was normotensive and normokalemic. The question is, whether this was caused by different mutations - genetic analysis was only performed in the elder sister - or whether the phenotype was different. It is known, that the phenotype can sometimes vary in patients with same mutations. Since until now in patients with P450c17 deficiency, always the same mutation occured in one family, we assume that in our two patients, just the phenotype is different.

The high gonadotropin levels indicated a primary defect in gonadal function and the low inhibin B reflected defective Sertoli cell function[6]. The enzyme deficiency is very likely, not only responsible for a disturbed sex hormone secretion, but may have also affected the production of the gonadal peptide hormones (inhibin B and AMH). AMH production by the Sertoli cells remains high throughout childhood in males but declines to low levels during puberty and the adult life. In our patients, AMH was normal for adult males, but subnormal for prepubertal male patients. Nevertheless, the absence of the uterus suggests the presence of the AMH during fetal life, because AMH prevents the development of the Mullerian ducts into the uterus.

The intra-abdominal testes must be removed. Glucocorticoid replacement reverses the DOC-induced hypertension and hypokalemia but this should be cautiously made to avoid hyperkalemia[1].

Additional sex hormones replacement is generally required from puberty onward. It has to be carefully performed, because the estrogen treatment may potentially influence the activity of the enzyme and can increase blood pressure[2].

CONCLUSION

A P450c17 deficiency is a very rare cause of 46, XY disorders of sex development. It is strongly supported by the discovery of the lack of secondary sex characteristics at puberty, hypertension and hypokalemia. Serum concentrations of gonadal steroids, cortisol and 17OH-progesterone are low and those of ACTH, progesterone, DOC and corticosterone are high. Gonadal peptide hormones (inhibin B and AMH) are also affected. Glucocorticoid and at puberty appropriate gonadal replacement is indicated.

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Case Report

Anaesthesia in a Patient of Severe Bicuspsid Aortic Stenosis for Caeserian Section

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ABSTRACT

An asymptomatic parturient with mild aortic stenosis (AS) and normal ventricular function may carry pregnancy to term and have a vaginal delivery. But severe aortic stenosis in a pregnant woman may result in rapid clinical deterioration associated with fetal and maternal mortality. Such patients may require treatment of AS before conception or during pregnancy, preferably during the 2nd trimester. Our patient presented with 34 weeks of amenorrhea and severe bicuspid AS was posted for elective lower segment cesarean section (LSCS). We present a case report describing the management of this challenging condition under balanced general anesthesia.

KEY WORDS: general anesthesia, lower segment cesarean section, parturient, systemic vascular resistance

INTRODUCTION

Aortic stenosis (AS) is uncommon during pregnancy as most patients with bicuspid valves, who develop stenosis, do so after the age of 50 - 60 years[1]. In AS, trans-valvular pressure gradient increases progressively throughout pregnancy due to increasing blood volume and decreasing systemic vascular resistance. The maternal as well as perinatal mortality are reported to be as high as 17.4% and 31.6% respectively[1]. Thus, understanding the physiology of pregnancy and the patho-physiology of the underlying cardiac disease is important when providing anesthesia for these high risk obstetric patients.

CASE HISTORY

A 24-year-old female weighing 57 kg with 34 wks of amenorrhea and severe bicuspid AS was admitted into our high risk pregnancy institute for elective lower segment cesarean section (LSCS). The patient was thoroughly assessed and investigated with all routine investigations. Her 2D Echo report showed a bicuspid aortic valve, severe AS, moderate aortic regurgitation (AR), concentric left ventricular hypertrophy (LVH) and mild pulmonary hypertension (PAH). Her ejection fraction was 55%. Her pre-operative vitals were as follows: pulse rate 90/min, blood pressure 100/60 mmHg. Her routine blood investigations were within normal limits. A cardiology consult was asked for. A plan for an elective LSCS, infective endocarditis prophylaxis (IE) and in the event of clinical deterioration in 3rd trimester, a balloon aortic valvotomy (BAV) was advised.

On the day of the elective LSCS, IE prophylaxis was given. Patient was premedicated with inj. ondansetron 8 mg, inj. ranitidine 150 mg, inj. glycopyrollate 0.2 mg. Non-invasive monitoring like a 3-lead electrocardiography (ECG), noninvasive blood pressure (NIBP) and pulse oximetry were applied. Invasive arterial blood pressure monitoring was done by cannulating the radial artery under local anesthesia. The patient was pre-oxygenated with 100% oxygen for three minutes. Anesthesia was induced with injection thiopental sodium and for the ease of intubation inj. succinylcholine was given. Gentle laryngoscopy was

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done and patient was intubated with a disposable portex cuffed endotraceal tube no. 7 within 15 seconds. The anesthesia was maintained with oxygen, isoflurane and inj. vecuronium. The hemodynamic parameters remained stable throughout the procedure. A male baby weighing 2.5 kg with an Apgar score of 7 at one minute and 10 at five minutes was delivered. The baby cried immediately after birth. Simultaneously, uterine muscle tone was achieved with oxytocin infusion (10 units/hr) and intramuscular prostaglandin (0.25 μg). Inj. Fentanyl 100 micrograms was given after delivery of baby.

The mother was extubated uneventfully and shifted to our high dependency unit (HDU) with continuous monitoring of vital signs. For post-operative analgesia, inj. diclofenac sodium 75 mg im was given 8-hourly. The patient was observed for one day in the HDU and shifted to her room in a hemodynamically stable condition.

DISCUSSION

Experience with pregnancy in patients with congenital bicuspid AS is more commonly found in men and severe stenosis is unusual in women of childbearing age. Severe critical AS is an important non-obstetric cause of maternal and fetal morbidity and mortality during pregnancy[2].

Symptomatic patient with critical AS should be appropriately counseled for delaying conception, until treatment of AS can be obtained. If cardiac surgery is necessary in a pregnant woman, it should be undertaken as early as possible in the gestation, preferably in the second trimester after the completion of organogenesis. But, if AS progresses to cardiac decompensation or infective endocarditis and presents with congestive heart failure (CHF), then balloon atrial valvotomy (BAV) or atrial valve replacement should be considered as life saving procedure before labor and delivery[3-5].

Our patient presented with severe bicuspid AS at 34 wks of pregnancy. She was on medical therapy which included, beta -blockers and diuretics. Because of her critical cardiac condition, a cardiologist's opinion was taken. They advised her to go for elective LSCS with IE prophylaxis, and if the patient deteriorated in the 3rd trimester, then BAV may be required.

Our goal was to manage this patient in a hemodynamically stable condition, *i.e.,* to maintain normal sinus rhythm, normal heart rate, to preserve cardiac contractility, avoid myocardial depression and maintain preload and systemic vascular resistance. In preventing maternal mortality due to AS, one has to keep in mind the progressive nature of severe AS and the fixed cardiac output which does not increase during uterine contraction, thus throwing the patient into severe decompensation and sudden cardiac death.

General anesthesia is often selected in preference to regional (epidural or spinal) anesthesia because the sympathetic blockade produced by regional anesthesia can lead to significant hypotension. Nevertheless, controversies do exist as for the careful titration of regional anesthetic technique that might provide a favorable hemodynamic profile. Continuous spinal anesthesia avoids many of the disadvantages of general anesthesia like hemodynamic perturbations of direct laryngoscopy and intubation. The use of volatile anesthetics leads to peripheral vasodilatation, myocardial depression and loss of normal systole. However, continuous spinal anesthesia has potential complications; it should be used with caution in patients in whom a difficult endotracheal intubation is anticipated. Peripheral sympathetic nervous system blockade produced by continuous spinal anesthesia may be deleterious in situations of profound blood loss. This is especially true in the setting of AS, where precipitous decreases in systemic vascular resistance can lead to the catastrophic cycle of hypotension-induced ischemia, subsequent ventricular dysfunction, and worsening hypotension. AS is often complicated by global ventricular hypokinesis and atrial fibrillation (AF). These patients are often anticoagulated and continuous spinal anesthesia would then be contraindicated[6]. One disadvantage of general anesthesia is the sympathetic nervous system response to intubation, which can generate tachycardia and hypertension, leading to sudden fluctuations in cardiac output. This can be controlled by induction with a cardio-stable drug that does not decrease the systemic vascular resistance such as etomidate. However, this drug was not available in our institute. Opioids may be useful, if left ventricular function is compromised. Maintenance of anesthesia can be done with a combination of nitrous oxide in oxygen and a volatile anesthetic and opioids or by opioids alone. Neuromuscular blocking drugs with minimal hemodynamic effects (like vecuronium or rocuronium) are best used[6-8].

Intravascular volume should be maintained at normal levels. A central venous catheter is desirable for assessment of preload. However, this was not inserted as the surgical procedure was of a short duration and no major fluid shifts were expected. The onset of junctional rhythm or bradycardia during anesthesia and surgery requires treatment with glycopyrolate, atropine or ephedrine. Persistent tachycardia can be treated with beta-blockers such as esmolol. Supraventricular tachycardia should be promptly terminated with electrical cardioversion. Inj. Lignocaine and a defibrillator should be kept available as these patients have a propensity to develop

ventricular dysrhythmias. Patients with AS remain at increased risk in the postoperative period. In 2001, the Report of the National Confidential Enquiry into Perioperative Deaths (CEPOD) recommended that in patients with an aortic valve area < 1 cm^2, particularly in association with a reduced ejection fraction, should have postoperative invasive monitoring in a HDU setting and excellent postoperative pain control[9].

According to one study, there was a higher incidence of maternal CHF and arrhythmias. There is a need to initiate or increase the dose of cardiac medications and hospitalization in patients with severe AS. Similarly, fetal outcome also seems to be affected by the presence of moderate to severe AS as suggested by a higher incidence of preterm birth, IUGR and low birth weight[10].

The stenotic valve leads to LVH and eventual myocardial ischemia, and there is a fixed cardiac output. So, hemodynamic stability is essential in the safe anesthetic management of patients with AS. In preventing maternal mortality one has to keep in mind the progressive nature of severe AS and the fixed cardiac output which does not increase during uterine contraction, thus throwing the patient into severe decompensation and sudden cardiac death[1]. Therefore, regular antenatal checkup and echocardiography in the first trimester which is repeated at least once in 2nd and 3rd trimester are required.

CONCLUSION

Management of pregnancy complicated by AS requires an accurate assessment of the severity of disease, because clinical symptoms appear very late in the course of disease. Therefore, regular antenatal follow-up with an obstetrician, cardiologist and anesthetist is required. Thorough knowledge and multidisciplinary team-based plan should be applied. We managed this high risk patient under balanced general anesthesia uneventfully and without any complication.

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Case Report

Nephrogenic Adenoma of the Urethra: A Rare Tumor in Children

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ABSTRACT

Nephrogenic adenoma (NA), an example of non-neoplastic epithelial abnormalities, is a rare reactive lesion that is capable of mimicking a tumor on cystoscopic examination and found mostly in bladder and also structures lined with urothelium such as ureter and urethra. A diagnostic cystoscopy was performed on a 16-year-old male patient admitted to our emergency department with the complaint of passing blood in the urine for a week. Multiple papillary structures, largest one reaching 5 - 6 mm in diameter, with active hemorrhage were observed in posterior urethra upon cystoscopy. A transurethral resection was carried out. A diagnosis of NA was made as a result of histopathologic studies. The patient presented two weeks later, stating that the hematuria was not resolved. A second transurethral resection was carried out after active haemorrhagic lesions were observed in the posterior urethra during cystoscopy. The patient currently has no complaint of hematuria, and is being followed-up. It should be kept in mind that nephrogenic adenomas located in urethra can be encountered during a cystoscopy in pediatric cases with hematuria. Cystoscopic examinations at regular intervals are thought to be effective in order to prevent local recurrence.

KEY WORDS: cystoscopy, dysuria, genitourinary trauma, hematuria, transurethral resection

INTRODUCTION

Nephrogenic adenoma (NA) is a tumoral lesion which is mostly seen in adults, first described as a hamartoma by Davis in 1949[1]. It was named as NA by Friedman and Kuhlenbeck in 1950 and the renal tubular structure was shown histologically. Seen mostly in bladder among adult cases, the lesion is also found in urethra (15%) and ureter and renal pelvis, less frequently[2]. It is very rare for a NA to be detected in children and in urethra as localization[3].

We present a case of 16-year-old male patient admitted to hospital with a complaint of hematuria and without the history of a urogenital trauma.

CASE REPORT

A 16-year-old male patient was admitted to our emergency department with 1-week history of passing blood in the urine. He had no former medical history for an existing disease, drug use, urogenital surgery or trauma. No pathology was observed on urinary ultrasonography (USG). A diagnostic cystoscopy was planned. Multiple papillary structures, largest one reaching 5 - 6 mm in diameter, with active hemorrhage were observed in posterior urethra upon cystoscopy (Fig 1). A transurethral resection was carried out. No similar pathology was observed in the bladder or other regions of urethra. A diagnosis of nephrogenic adenoma was made as a result of histopathologic studies. In light microscopic examination, the hematoxylin-eosin stained section has shown small nodular mass composed of small tubules lined by single layer of cuboidal, spindle or hobnail cells. Some dilated tubules have filled with eosinophilic granular material. The cells have had eosinophilic cytoplasm and minimal atypical nucleus (Fig 2). The cells cytoplasm and some tubular lumens have stained with periodic acid schiff (Fig 3). In addition, cytoplasmic and apical membranous immunohistochemical MUC1 positivity in tubules supported the diagnosis, nephrogenic adenoma (Fig 4). At a follow-up visit two weeks later,

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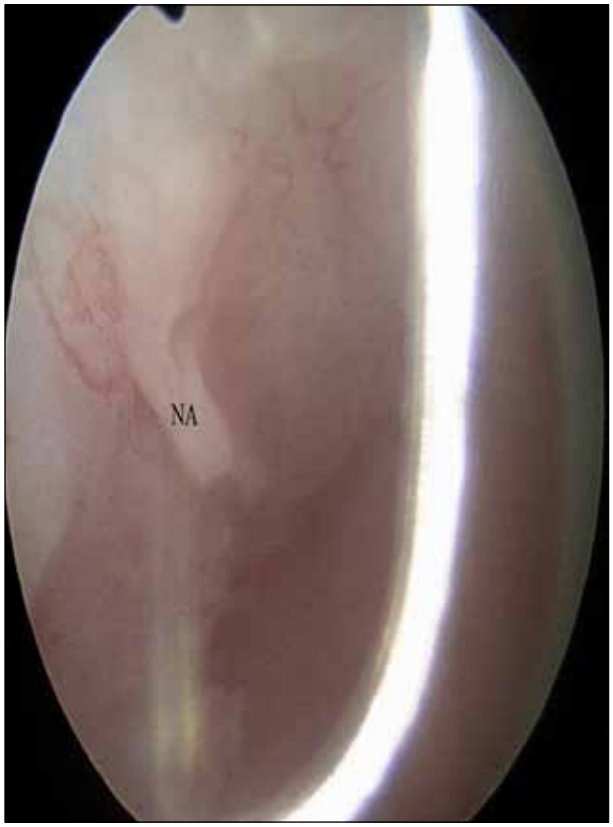

Fig 1: The cystoscopic apperance of NA in the urethra.
NA: Nephrogenic Adeoma

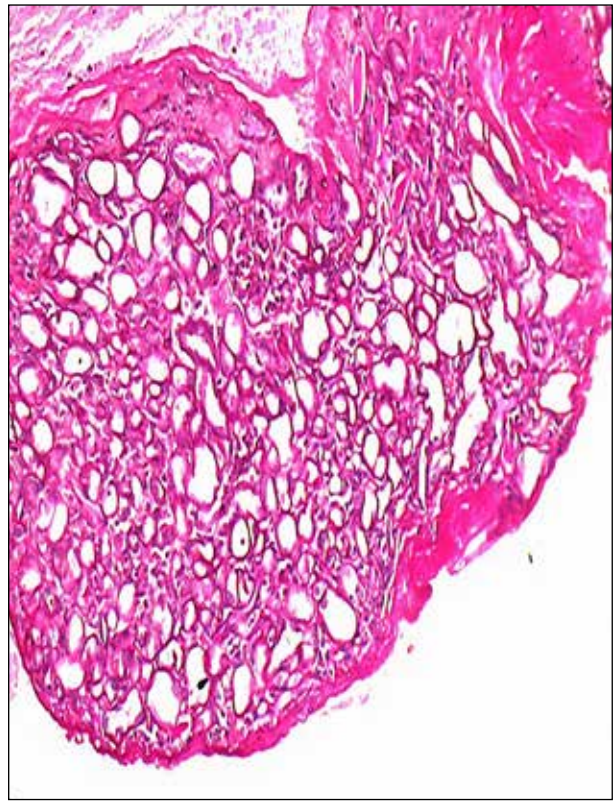

Fig 3: The positivity of the cells cytoplasm and tubuler lumens with periodic acid schiff histochemical staining. Periodic Acid Schiff, x100

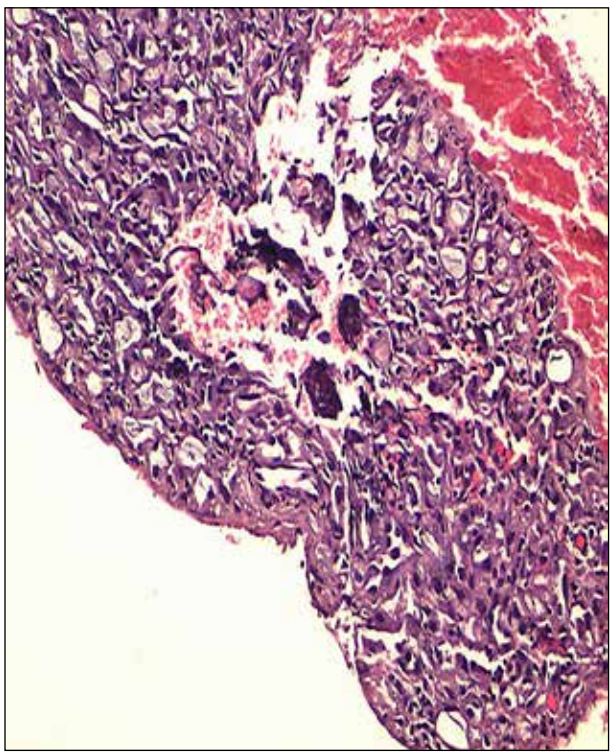

Fig 2: The microscopic apperance of the small nodular mass composed of small tubules lined by single layer of cuboidal,spindle or hobnail cells. Hematoxylin Eosin, x100

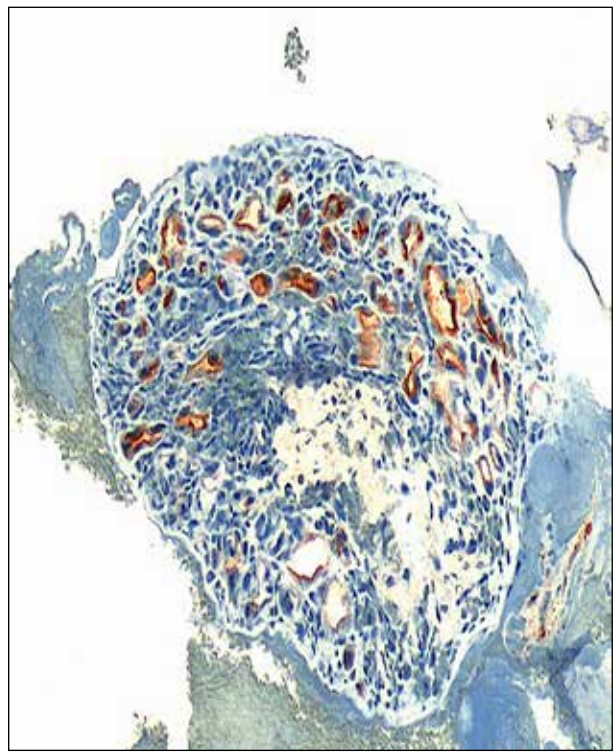

Fig 4: The cytoplasmic and apical membranous MUC1 positivity in tubules. MUC1, x100

the patient stated that his complaints (dysuria and hematuria) were not completely resolved. A control cystoscopy was performed. Active hemorrhagic lesions were seen in the posterior urethra. We thought that the recurrence of hematuria after two weeks might be due to the fact that the first transurethral resection was incomplete.The patient stated that his complaints did not resolve when he came for a follow-up visit after two weeks. A follow-up cystoscopy was performed. Transurethral resection was repeated. Complaints of the patient, who had a total of two transurethral resections done, completely resolved and he is being monitored by follow-up visits. A control cystoscopy is planned in three months to detect any potential recurrence.

DISCUSSION

Nephrogenic adenoma is seen more frequently in males among adults with a ratio of 3:1, whereas it is seen three times frequently in females than males in childhood[1]. The most common findings are dysuria and hematuria[4]. Known predisposing factors are genitourinary trauma, surgery, chronic inflammation, urinary tract stones and pelvic radiation[5]. Also it is stated that that nephrogenic adenomas are associated with phenacetin, ibuprofen usage and BCG application for the treatment of carcinomas of the urinary system. NA lesions show a tendency towards local recurrence. Although NA is widely accepted as a benign lesion, malignant transformation occurs frequently in immunocompromised patients. Two different theories about pathogenesis of NA have been put forward. According to the first theory, NA originates from embryogenic mesonephric vestiges. The second theory claims that it is formed due to a metaplasia caused by the inflammation secondary to a trauma[1]. Our case suggests the first theory, since he has no former medical history of drug use or surgery. Although most NA are smaller than 1 cm, 10% are larger than 4 cm in diameter[1]. In our case, they were observed as a papillary structure smaller than 1 cm. The lesion is usually seen as single or multifocal papillary structures[5]. Macroscopic growth patterns are tubular, tubulocystic, papillary or polypoid. Small and medium sized tubules and basement membrane around them can be seen on histological examination. Acidophilic and basophilic secretions of these tubules can be also observed[1].

In adults, prostatic adenocarcinoma and clear cell adenocarcinoma; in children rhabdomyosarcoma and transitional cell carcinoma should be considered in differential diagnosis[2]. USG, cystoscopy and histological examination are used in diagnosis. Treatment procedure involves cauterization of the tumor base following a transurethral resection but the recurrence rate is 37.5%[5]. Low-dose usage of antibiotics is suggested in long term therapy to prevent urinary system infection[1,4]. Routine cycstoscopic examinations at a regular interval of three months are recommended for early detection of recurrence and malignant transformation[1]. After a substantial disease-free period, cystoscopy should be carried out every six to twelve months. Cystoscopic examination should be done more frequently in patients with clinical symptoms. Repetitive cystoscopy creates an increased risk of recurrence of NA[6].

CONCLUSION

A nephrogenic adenoma located in urethra was detected in our case, who did not have any history of trauma. Therefore, it should not be forgotten that NA of the urethra can be encountered in pediatric cases admitted with hematuria at early age. Also cystoscopic examinations at regular intervals are thought to be effective in order to prevent local recurrence.

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Case Report

Pregnancy after Radical Vaginal Trachelectomy followed by Chemotherapy in Small Cell Neuroendocrine Carcinoma of the Cervix: A Case Report and Literature Review

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ABSTRACT

Small cell neuroendocrine carcinoma of the cervix (SCNCC) is a very rare cervical malignancy with poor prognosis and increasing number of women are being diagnosed with SCNCC at a younger age. Few reports showed patients with childbearing age were treated with radical trachelectomy followed by chemotherapy. We report a 37-year-old woman with SCNCC who was treated with radical vaginal trachelectomy followed by six cycles of chemotherapy. The patient became pregnant after receiving assisted reproductive technology, but ended with a first trimester miscarriage. We discuss here our experience and recognize that radical vaginal trachelectomy followed by chemotherapy may become an effective option for younger women with SCNCC who wish to preserve their fertility potential.

KEY WORDS: cervical malignancy, miscarriage, pregnancy, lymph node metastases, vascular invasion

INTRODUCTION

Small cell neuroendocrine carcinoma of the cervix (SCNCC) was first described in 1957[1]. The diagnosis of SCNCC requires the presence of small round or fusiform cells with scanty cytoplasm, frequent mitoses, hyperchromatic nuclei having finely granular chromatin, and absent or inconspicuous nucleoli, with or without positive staining of neuroendocrine markers[2]. SCNCC is a very rare finding, representing less than 5% of all cervical malignancies. The mean annual incidence of SCNCC according to a former report was 0.06 per 100,000 women[3]. It is extremely aggressive and has an unfavorable outcome, because of the early development of lymph node metastases and vascular invasion[4]. Due to small number of cases, treatment strategies have not been established so far, let alone for the women with childbearing age who wish to preserve their fertility. We experienced one case of small cell neuroendocrine carcinoma of the cervix, who underwent radical vaginal trachelectomy and laparoscopic pelvic lymphadenectomy followed by six cycles of chemotherapy, and eight gestational weeks of pregnancy after assisted reproductive technology, ended with spontaneous abortion. We report this case together with a literature-based discussion.

CASE REPORT

A 37-year-old healthy nulliparous woman, gravida 3, para 0, with infertility for two years, presented to gynecology with a 1-month history of postcoital bleeding in January 2011. Initial physical examination revealed no signs of cervical mass, except abnormal papsmear. Cervical biopsy demonstrated small cell neuroendocrine carcinoma of the cervix. High-risk oncogenic HPV type was detected positive. Complete blood count, blood chemistry and chest X-ray were normal. Clinical staging according to the International Federation of Gynecology and Obstetrics (FIGO) classification was stage Ia2. The patient desired to conserve fertility despite of the poor prognosis.The

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option of trachelectomy was discussed. The patient received radical vaginal trachelectomy (RVT) and laparoscopic pelvic lymphadenectomy. The RVT was performed to remove two-thirds of the cervix with a small vaginal cuff and a third of the neighboring parametrium.There were no complications during or after surgery. The margin of cervix and lymph nodes (total of 32 nodes) were negative for tumor. Diagnosis was confirmed by immunohistochemical staining (positive immunoreactivity for chromogranin A and synaptophysin and neuronal cell adhesion molecules (CD56) (Fig 1 and 2). After surgery, chemotherapy was administered in the form of six cycles of chemotherapy combined of lobaplatin 50 mg day 1 and etoposide 100 mg day 1 - 3 every 3 - 4 weeks. Four months after the surgery, the patient had regular cycles of menstruation. Six months after the last cycle of chemotherapy, 10 months after the surgery, the patient became pregnant in December 2011 with the

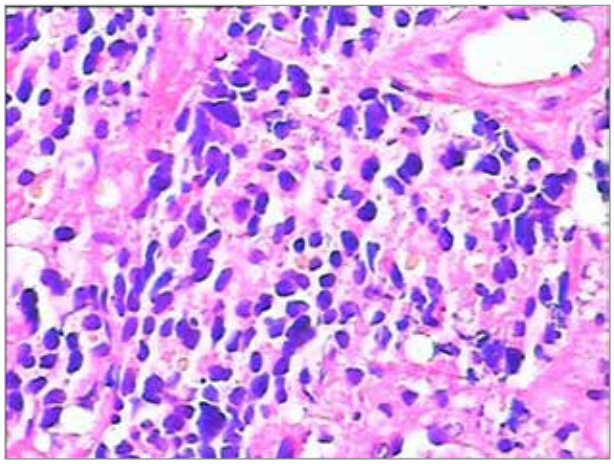

Fig 1: Microscopic examination revealing small irregular nests of neoplastic cells (hematoxylin and eosin, x 400).

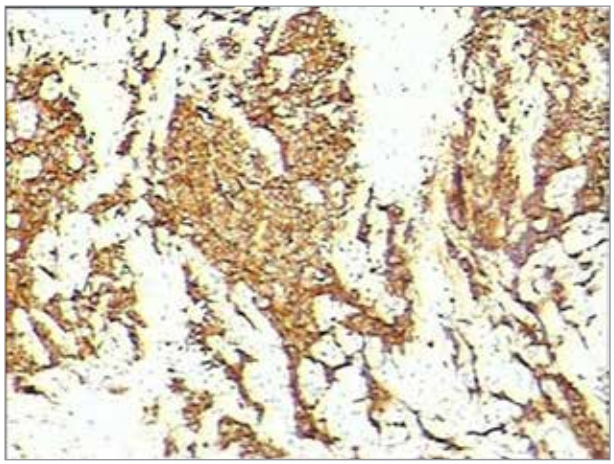

Fig 2: IHC stains. Tumor cells with diffuse, strong staining for neuronal cell adhesion molecules (immunoperoxydase × 100).

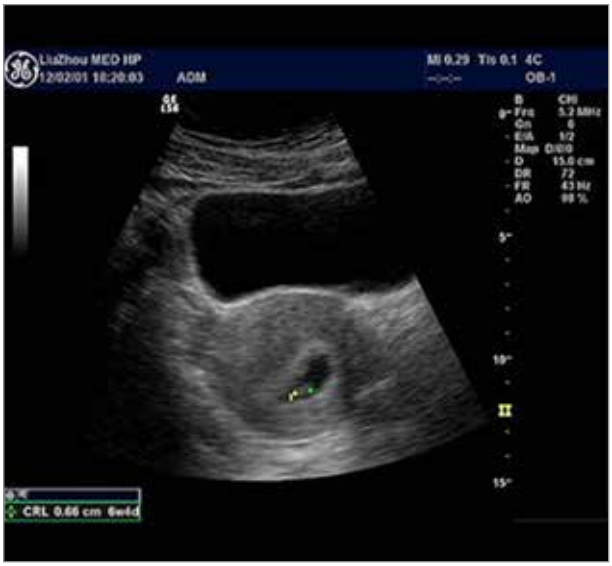

Fig 3: The fetal heart beat at 6 gestational weeks after receiving assisted reproductive technology.

attempt of in vitro fertilization (Fig 3, which was ended with spontaneous abortion at eight gestational weeks in February 2012. Follow-up was performed every 3 - 4 months) Upon writing no recurrent signs have been observed for 26 months after diagnosis.

DISCUSSION

Small cell neuroendocrine carcinoma of the cervix (SCNCC) is a very rare cervical malignancy, patients diagnosed with small cell neuroendocrine carcinoma of the cervix are more likely to have early lymph node metastases and lymph vascular space invasion with poor progonosis .The vast majority of patients present with vaginal bleeding[5].

The diagnosis of SCNCC has been improved currently by using of immunostaining to identify general neuroendocrine markers including: neuron-specific enolase, chromogramin A and synaptophysin[6]. In many case reports that evaluated markers, all of the specimens stained positive for at least one of the various markers[5]. In the present case, chromogramin A, synaptophysin and neuronal cell adhesion molecules (CD56) were positive. However, as indicated by the work-shop sponsored by the College of American Pathologists and the National Cancer Institute, not all of the markers need to be present to confirm the diagnosis, because 60% are negative for chromogramin A and synaptophisin, and 30% for neuron-specific enolase[7]. Therefore, other methods such as electron microscope is recommended for diagnosis.

Small cell neuroendocrine carcinoma of the cervix is associated with poor prognosis. Recurrences

reported in the literature occurred earlier than 35 months after diagnosis[8] .The 5-year survival rate of patients with FIGO stage IB1 disease was reported between 50 - 60%, which was significantly less than the 90% rate for patients with stage IB1 squamous cell carcinoma [8]. Jergin Chen *et al* [3] stated the actuarial overall survival for women with small cell carcinoma of the cervix was 46.8%, 35.7%, and 28.3% at 2, 5, and 10 years respectively, which was significantly worse than for squamous cell carcinoma of the cervix and adenocarcinoma of the cervix by stage adjusted log-rank test. New research suggests that those with stage I-IIA disease had a 5-year survival of 36.8% compared with 9.8% for those with stage IIB-IVA and 0.0% for those with stage IVB[9].

In cases of SCNCC, the standard modality of therapy remains controversial. The Gynecologic Oncology Group attempted to study small cell cervical carcinoma in protocol 66 between 1982 and 1986, but failed to recruit sufficient numbers of patients[10]. Pelvic control alone such as radical hysterectomy and radiotherapy does not usually lead to a good outcome because of the high incidence of distant metastasis in early stage. Although there are few clinical studies supporting the use of adjuvant multimodality treatment in early-stage SCNCC, most authors favor the use of chemotherapy because of the high incidence of distant metastases[8]. The optimal chemotherapy is difficult to distinguish due to limited cases. Cohen JG *et al*[9] analysed 188 cases of small cell carcinoma of the cervix and showed that cisplatin combined with etoposide appears to be the most commonly used regimen. In the present case, lobaplatin instead of cisplatin was selected in order to reduce side-effects, which proved to be effective considering no recurrence to be observed with no side effects.

Huang CY *et al* [10] reported in a population-based study of cervical cancer in Taiwan from 1991 to 2005, the incidence of small cell cervical carcinoma tended to increase. However, the incidence of squamous cell carcinoma significantly decreased from 1990 to 2005. The study also indicated a significantly younger mean age from 20 to 29 at diagnosis for small cell cervical carcinoma compared to squamous cell or papillary carcinoma. Many of these patients are of childbearing age and wish to preserve their fertility, which makes radical trachelectomy be necessary. However, the previous study stated these patients with SCNCC should probably not be offered fertility-sparing surgery for the aggressive variant[11]. In the present case, the patient desired intensively to conserve fertility despite of the poor prognosis, and received radical vaginal trachelectomy followed by chemotherapy instead of radical hysterectomy and radiotherapy, which proved to be effective.

Radical vaginal trachelectomy (RVT) is a unique procedure developed by Daniel Dargent and others, which is based on the technique of radical vaginal hysterectomy[12]. It has been used primarily for cervical carcinoma and offers the ability to potentially preserve fertility in younger women desiring of that option. Few reports showed the patient of SCNCC was childbearing age treated with radical trachelectomy, l*et al*one the report of the outcome of pregnancy after radical trachelectomy. Roy M *et al* has reported 37 patients treated by RVT with 42 months follow-up, two patients recurred including one who had a small-cell neuroendocrine tumor[13]. In two cases of SCNCC, radical trachelectomy without adjuvant chemotherapy led to short term recurrence and early death, which suggested that radical trachelectomy only for patients with early stage SCNCC is not appropriate.

In the present case, the patient was treated with radical vaginal trachelectomy followed by six cycles of chemotherapy with excellent outcome. Up to now, she has had no evidence of recurrence or metastasis after 26-months follow-up. The patient became pregnant after in vitro fertilization. Unfortunately, she ended up with spontaneous abortion with a first trimester miscarriage, and the reason of miscarriage was still not claer. Speiser D *et al*[14] found that the rate of first-trimester miscarriages after radical vaginal trachelectomy (8.3%) was not higher than that in the general population (approximately 14 - 20%) in their cohort. Concerning fertility outcome, premature labor is the main problem. Standardized preventive management for pregnant women after RVT might be beneficial.

CONCLUSION

SCNCC is a type of tumor associated with poor outcomes and the best modality of treatment for women of childbearing age remains controversial. To the best of our knowledge, this is the first case report about pregnancy after radical vaginal trachelectomy followed by chemotherapy of SCNCC. Radical vaginal trachelectomy followed by chemotherapy might be an effective option for younger women, who wish to preserve their fertility potential. It would therefore, need more data to corroborate.

ACKNOWLEDGMENT

Conflict of interest: All authors declare no conflict of interest in this study.

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Case Report

FNAC Diagnosis of Granular Cell Tumor: A Case Report

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ABSTRACT

Granular cell tumors (GCT) are uncommon neoplasms which have been described to occur at many diverse sites throughout the body. The authors take this opportunity to report a case of granular cell tumor, diagnosed on FNAC and later confirmed on histopathology as granular cell tumor - unknown malignant potential. The recurrence of the tumor was also diagnosed by FNAC. The review of literature is also done.

KEYWORDS: benign neoplasm, granular cytoplasm, mitoses, necrosis

INTRODUCTION

Granular cell tumor (GCT) is an uncommon benign neoplasm of neural histogenesis, although initially it was described as a tumor of muscle derivation[1]. These are characterized morphologically by tumor cells with abundant granular cytoplasm and are hence named so. Although majority follows a benign course, cases with malignant behavior have also been described. Apart from benign and malignant, there also lies a grey zone which has high potential for local aggressiveness and metastasis[2]. The histopathological features of GCT are well described, but diagnosis based on cytological findings alone is not so common. However, with proper approach and sound knowledge, cytological findings can aid in the early diagnosis of GCT, as is evident from Table 1.

CASE REPORT

A 23-year-old female presented to our hospital with the complaint of a swelling on the dorsal aspect of right foot since six months. It was not associated with any pain or any history of trauma. On examination, the swelling was subcutaneous, firm, non tender, round to oval in shape, non pulsatile and non compressible, measuring 4 cm in diameter. It was adherent to the skin. General and systemic examinations were unremarkable with no evidence of any lymphadenopathy. Hemogram, blood sugar, renal function test, and chest X-ray were within normal limits.

Fine needle aspiration cytology (FNAC) from the swelling was performed by 25 gauge needle. Smears showed low cellularity of epithelioid to spindle cells with abundant granular cytoplasm and having rounded paracentral nuclei with small prominent nucleoli (Fig 1). Granular material and naked nuclei were also present in the background. A tentative diagnosis of granular cell tumor was given.

Surgical excision of the swelling was done and the excised tissue was sent for histopathological examination. Grossly, the tissue was a single whitish tissue piece; measuring 2.3 x 2.2 x 2 cm. Outer surface was unremarkable and cut surface was solid and white. The entire tissue was processed. On histopathological examination, the tumor was poorly circumscribed and mainly centered in the lower dermis and subcutaneous tissue. The neoplasm was composed of multiple fascicles and sheets of epithelioid to spindle cells with abundant granular cytoplasm and scattered <2 mitotic figures per 10 high power fields (Fig 2). Nuclear to cytoplasmic ratio was not increased with moderate degree of nuclear pleomorphism with focal evidence of necrosis. On immunohistochemistry (IHC), the tumor cells were positive for S100 (Fig 3) and CD68; negative for SMA, desmin, and Myo-D1. A final diagnosis of granular cell tumor of unknown malignant potential was rendered and a close follow up was advised.

After 11 months, the patient presented again to the surgical out-patient department with a nodule measuring about 1 x 1 cm at the site of prior surgery. This time, the differential was tumor recurrence versus

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Table 1: Comparative analysis of the clinico-pathological features in Granular cell Tumor publications

Study	Age (Years)	Sex	Site	Size (Centimeter)	Cyto-diagnosis	Histo-diagnosis	IHC	Recurrence
Singh *et al*[3]	40	Male	Right forearm	3.2 × 2.1 × 1	GCT	GCT	S100+	No data
Mallik *et al*[4]	7	Female	Right forearm	2 x 3	GCT	GCT	S100+	No data
Akatsu *et al*[5]	53	Female	Left breast	2.8 x 2.7	GCT benign	GCT (benign)	S100+, NSE+, vimentin+, Desmin-, SMA-, EMA-, CEA -	No
Pathania *et al*[6]	58	Female	Right breast	3 x 2 x 2	GCT Benign	GCT (benign)	S100+	No data
Toi *et al*[7]	37	Female	Left lower back	2.5 x 2.5	Xanthogranuloma	GCT	S100+, CD68+, NSE+	No data
Toi *et al*[7]	53	Female	Anterior abdominal wall	3 x 2	GCT	GCT	S100+, CD68+, NSE+	No data
Liu *et al*[8]	70	Female	Left supra- clavicular lymph node/back	3	Metastatic GCT/ atypical GCT	Malignant GCT	S100+, vimentin + CK-, HMB45-, Mart 1-	No
Bean *et al*[9]	51	Male	Posterior mediastinal mass	4 x 2.8 x 2.5	GCT	GCT	S100+, CD68+	No data

GCT= Granular cell tumor, NSE= Non specific enolase, SMA = Smooth muscle actin, EMA = Epithelial membrane antigen, CEA = Carcinoembryonic antigen, CK = Cytokeratin

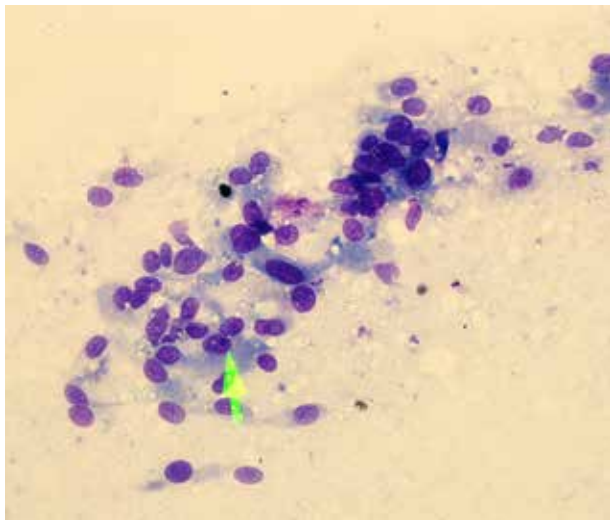

Fig 1: Smear showing epithelioid to spindle cells with abundant granular cytoplasm, round nuclei and prominent nucleoli (arrow) (Diff-quik x 400).

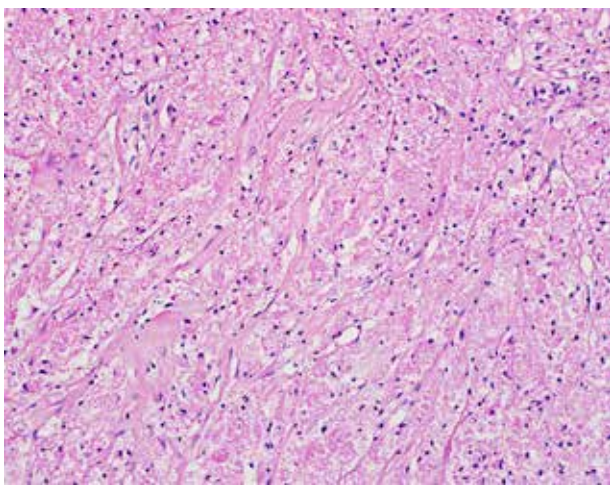

Fig 2: Section showing tumor composed of multiple fascicles of epithelioid to spindle cells with abundant granular cytoplasm (H&E x 100).

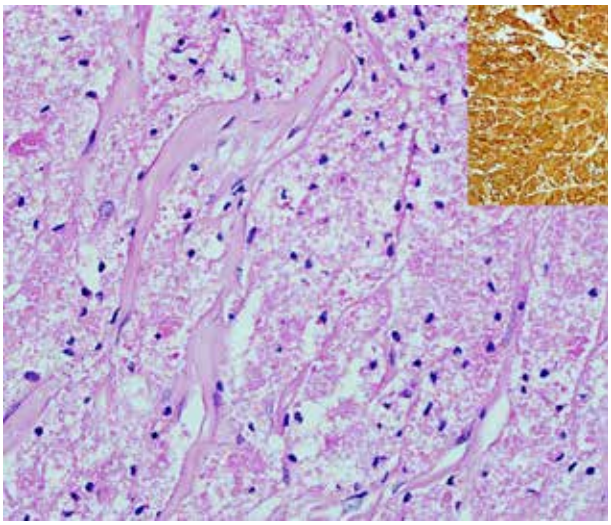

Fig 3: Section showing tumor composed of multiple fascicles of epithelioid to spindle cells with abundant granular cytoplasm (H&E x 400) with inset showing positivity to S100 (x 100).

scar nodule. FNAC was utilized to sample the nodule which revealed similar cytology as was seen the first time. There was no necrosis. However, there was an increase in the number of spindle cells as compared to epithelioid cells; a diagnosis of recurrent granular cell tumor was rendered.

DISCUSSION

GCT is a unique type of neoplasm characterized histologically by the presence of tumor cells having abundant granular cytoplasm. The most common location is the tongue; however, it can occur in many other locations like skin, vulva, breast, larynx, bronchus, esophagus, stomach, appendix, rectum, anus, bile ducts, pancreas, urinary bladder, uterus, brain, pituitary gland and soft tissues[10]. Rarely do these tumors occur on the feet, only eight cases have been reported in literature and all of them were diagnosed on histopathological examination. Ours

is the first case of GCT of foot being reported on FNAC in literature, to the best of our knowledge[11]. These tumors have a slight predilection for females, specially in the fourth to sixth decade and usually present as asymptomatic, slowly growing and poorly circumscribed nodules, which can be solitary or multiple[12].

The first case was described by Abrikossof in 1926[13]. The origin of these tumors remains controversial; studies have indicated its origin to be from Schwann cells or other perineural cells[1]. This theory is further supported by the location of these tumors, which is either near or within the peripheral nerves.[14]

FNA smears show loosely dispersed groups of large polygonal cells, without appreciable cell borders containing abundant granular and fragile cytoplasm, accompanied by stripped bare nuclei. Although rare in occurrence, as is evident from Table 1, GCT can be diagnosed on the basis of FNAC. The chief differential diagnosis on cytology remains histiocytic collection/fat necrosis which lack the characteristic abundant granular cytoplasm; the other differential diagnosis being alveolar soft part sarcoma, which has larger nuclei with prominent nucleoli and frequent binucleation. On histopathological examination, the tumor is composed of nests and masses of polygonal to round cells having abundant cytoplasm with coarse eosinophilic PAS positive granules[10]. Ultrastructurally, these granules are autophagic vacuoles containing mitochondria, myelin bundles, and rough endoplasmic reticulum as well as other cellular debris[15]. On immunohistochemistry, the tumor cells are positive for S100, vimentin, NSE, calretinin and CD68; negative for muscle markers[10,12].

Although majority of granular cell tumors behave in a benign fashion but few cases with metastasis and local aggressiveness have also been reported[2]. Fanburg-Smith *et al* (1988) proposed a three-tier classification and categorized granular cell tumor into benign, atypical and malignant[2]. However, Nasser *et al* (2011) refined the Fanburg-Smith classification. They based their classification only on two histological criteria – necrosis and mitoses. They categorized granular cell tumor into benign (having none of the criteria) and granular cell tumor-unknown malignant potential (having at least one of the two criteria) [16]. They considered metastasis as the only denominator for the malignant cases and concluded that a case of recurrent granular cell tumor of unknown malignant potential should be diagnosed as a case of granular cell tumor of unknown malignant potential, until there is evidence of metastasis[16], as has been the observation with present case.

Subcutaneous GCT should be differentiated from alveolar soft part sarcoma, rhabdomyoma, hibernoma and granular variant of squamous cell carcinoma. The cells of alveolar soft part sarcoma are strongly positive for muscle markers. Rhabdomyomas show the typical cross striations and stain strongly for myoglobin, desmin and muscle specific actin. Hibernomas are easily distinguished by the presence of intracellular oil red O positive lipid vacuoles. Granular cell tumor can often mimic granular variant of squamous cell carcinoma but is negative for CK5/6 and doesn't comprise of islands of malignant squamous cells[10,12].

Malignant granular cell tumors account for about 1 - 2% of all granular cell tumors.[16] Tumors typically spread via lymphatic and hematogenous routes to the lungs, liver, and bones. At times, metastasis was discovered after many years of surgical excision and therefore, a patient of granular cell tumor should have lifelong follow up[17]. The treatment of choice for all granular cell tumors is surgery. Radiation therapy and multi-agent chemotherapy generally do not improve prognosis[18].

CONCLUSION

FNAC is an easy, time saving and cost effective procedure which, with good awareness and right technique, can aid in the early diagnosis and prompt treatment of GCT.

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Case Report

Severe Hypertension during Transurethral Resection of a Bladder Tumor as a Result of an Undiagnosed Paraganglioma

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Kuwait Medical Journal 2016; 48 (2) : 162 - 165

ABSTRACT

A 59-year-old man presented with painless hematuria, urinary frequency, urgent micturition and dysuria was referred to the Urology Department. He had no history of hypertension or headaches associated with voiding. The patient was later diagnosed as having bladder tumor. During cystoscopy and resection of the bladder tumour, he developed severe, and difficult to control hypertension during surgery. Two days later, the resected bladder tumor was diagnosed by a pathologist to be a paraganglioma

KEY WORDS: cystoscopy, hematuria, micturition, paraganglioma

INTRODUCTION

Extra-adrenal paragangliomas are uncommon but are of particular interest to anesthesiologists as they can cause severe hemodynamic disturbances during surgery. Insufficient preparation preoperatively can lead to a very high mortality rate. Although they can arise in a variety of body sites, they are occasionally found in the kidney, spermatic cord, bladder, urethra and prostate[1]. In such circumstances, patients are often misdiagnosed. The anesthetic management of this condition is similar to that of pheochromocytoma, but the failure to diagnose paragangliomas preoperatively can lead to a mortality rate up to 50% of patients during surgery[2].

Fortunately, most patients may have related symptoms that are associated with micturition, including headaches, palpitations, hypertension, diaphoresis and blurred vision. We present a case in which the patient did not have any obvious related symptoms and the diagnosis of a paraganglioma was not made before surgery, which led to severe hemodynamic disturbances during the transurethral resection of the tumor.

CASE REPORT

A 59-year-old, 75 kg man with a history presenting complaints of painless hematuria, urinary frequency, urgent micturition and dysuria for the previous two days was referred to the urology department at our hospital. He had no history of hypertension or headaches associated with voiding. On admission, the systolic blood pressure was 120 mmHg and the diastolic pressure was 80 mmHg. His preoperative blood tests, including serum biochemistry and coagulation studies, were normal. A chest X-ray showed cardiomegaly and electrocardiography revealed left ventricular hypertrophy. Ultrasound Scan (US) showed an elevated lesion on the left wall of the urinary bladder that measured approximately 36 × 24 mm (Fig 1). At cystoscopy, a tumor was found at the 1 - 2 o'clock position on the urinary bladder wall. Computed tomography (CT) demonstrated a tumor that protruded approximately 52 × 35 mm into the lumen of the urinary bladder, but there was no evidence of tumor invasion into the adjacent organs (Fig 2). A bladder tumor was then diagnosed, and he gave consent for a transurethral resection under general anesthesia.

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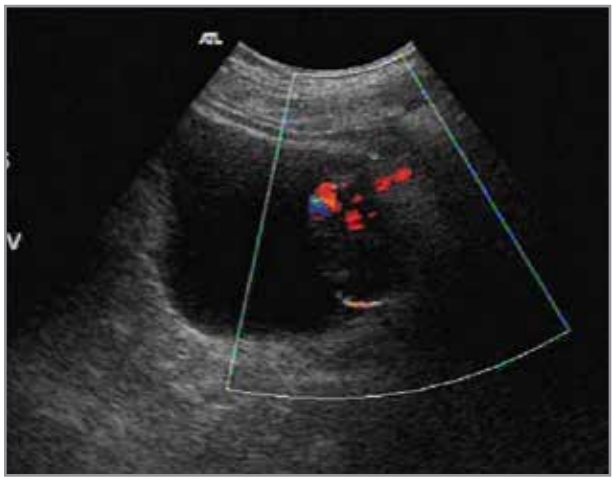
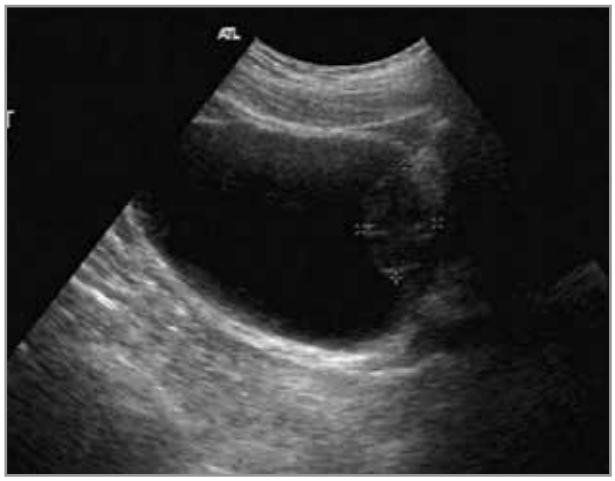

Fig 1a and 1b: Ultrasound appearance of the 36 ¡Á24-mm mass originating from the left lateral bladder wall with exuberant blood stream

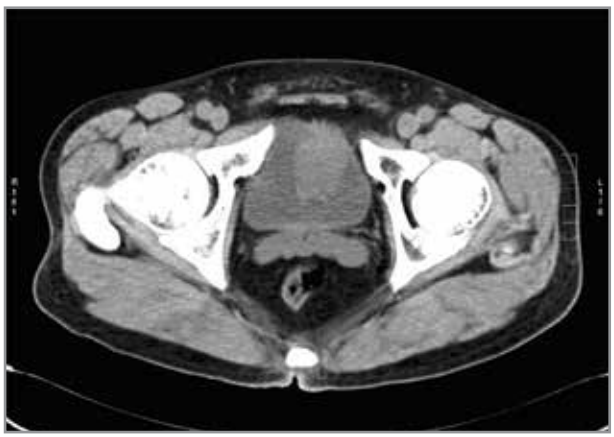
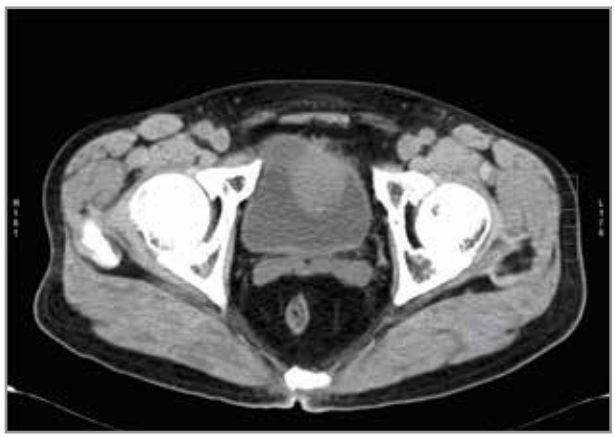

Fig 2a and 2b: Computed tomography revealing the mass originating from the left anterior and inferior bladder wall, with no evidence of tumor invasion into the adjacent organs

Intraoperatively, the patient was monitored with a continuous II lead ECG, pulse oximetry and noninvasive blood pressure monitoring every three minutes. The patient did not receive any premedication, and his blood pressure prior to induction was 150/90 mmHg with a heart rate of 66 bpm. After preoxygenation, intravenous (IV) anesthesia was induced smoothly with 0.1 mg fentanyl, 20 mg etomidate, and 6 mg cisatraronium. Approximately 90 seconds later, a number 4 sized laryngeal mask airway (LMA) was inserted. No skin rash or vital sign changes occurred after the induction of anesthesia. Maintenance anesthesia was commenced with propofol (5 mg/kg/h). His average blood pressure (BP) was 140/90 mmHg and heart rate (HR) 60-70 bpm prior to the commencement of surgery.

Before the incision, a further 0.1 mg fentanyl was added; however, just after the first incision was made, the patient's blood pressure increased to 240/125 mmHg, and his HR decreased from 80 bpm to 62 bpm. Noninvasive blood pressure monitoring was immediately changed to continuous monitoring. As we initially suspected that the anesthesia was not sufficiently deep, we administered a bolus of propofol and remifentanyl, but these did not alleviate the hypertension. The operation was immediately suspended and the patient was treated with 0.4 mg nicardipine. Within 1 min, his blood pressure had decreased to 140/88 mmHg.

Considering that there was a direct association between the tumor and the cause of the hypertension, we suggested that surgery should not continue; the tumor had already been incised, and the operation concluded after hemostasis was achieved. The hypertension persisted for approximately 4 min during surgery; however, his blood pressure decreased to approximately 130 - 140/80-90 mmHg just after the initial incision of the tumor. Two days later, the tumor was determined by a pathologist to be a paraganglioma (Fig 3). The patient was discharged from the hospital without hematuria on the third day postoperatively.

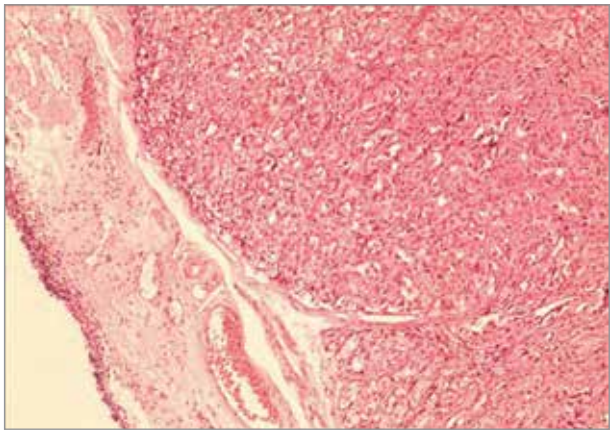

Fig 3a: The tumor cells were localized in the submucosa of the urinary bladder. The intersecting bundles of Schwann cell like-cells contained scattered ganglionic cells and they were separated by thin tumorous tissue containing capillaries. HE40

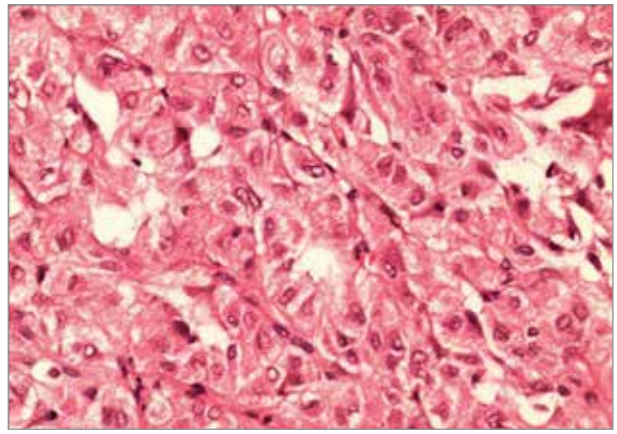

Fig. 3b: The tumor cells had plump cytoplasm and single distinct nucleoli. HE200

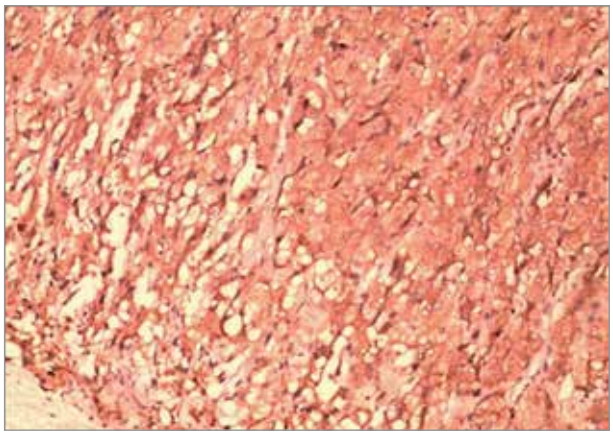

Fig 3c: CgA positive cells

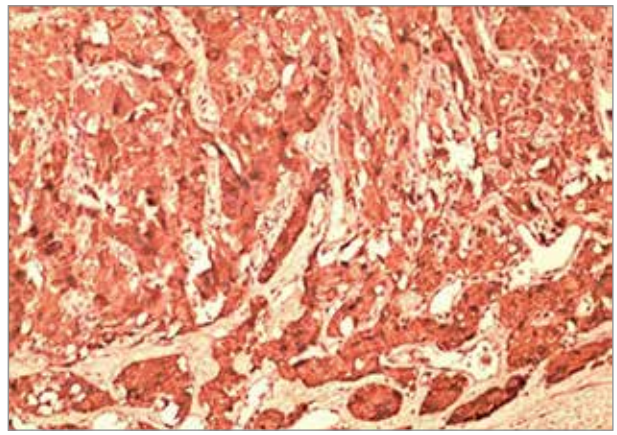

Fig 3d: Syn positive cell

DISCUSSION

Paragangliomas are tumors derived from the parasympathetic and sympathetic nervous systems[3]. Parasympathetic-associated paragangliomas that arise in the head and neck are usually nonfunctioning. The sympathetic-associated paragangliomas that arise from the adrenal medulla or from the sympathetic ganglia are generally functionally active, as indicated by excessive catecholamine production. The term pheochromocytoma is also currently applied to catecholamine-secreting paragangliomas that are intra-abdominal (adrenal or extra-adrenal) or thoracic[4]. Of all the paragangliomas, only a relatively small proportion produce catecholamines in sufficient amounts to produce signs and symptoms or positive results on biochemical testing[5].

Paragangliomas of the urinary bladder account for <0.5% of bladder tumors[6], and they usually occur in young adult women. They are commonly associated with hypertension and hematuria[7]. Some patients have palpitations or episodic headaches. According to Chi-Hang Kouk[8], headache, palpitations, and sweating in the presence of hypertension has high specificity (93.8%) and sensitivity (90.9%) for the diagnosis of pheochromocytoma. However, the present patient had no symptoms except hematuria, which may have been because the plasma concentration of epinephrine (E) and norepinephrine (NE) were subclinical. In retrospect, it is unfortunate that no laboratory data were available regarding serum and urinary catecholamine levels. Usuda and Emura reported the case of a patient with a paraganglioma who had no symptoms except dysuria, but with elevated levels of 24 h urinary excretion of E, NE and vanillylmandelic acid (VMA)[9]. In our case, the severe hypertension that appeared during surgery was likely due to large volumes of catecholamines released on the incision of the tumor. This type of tumor is usually located intramurally in the lateral and posterior wall of the bladder[7], which was consistent with the location of the tumor in the present patient.

The ability to distinguish between the diagnosis of paragangliomas, especially secreting paragangliomas, and urothelial cancer is important because of the very different anesthetic management strategies that are required. Undiagnosed secreting paragangliomas may bring great dangers to the patient, such as severe hypertension, arrhythmias and heart failure. However, paraganglioma of the urinary bladder is a rare tumor and only 13% of the cases are associated with preoperative symptoms [10], which makes it easy for them to be misdiagnosed as urothelial or bladder cancers. Certain clinical and gross features are useful in making this differential diagnosis. In general, patients are significantly younger than those diagnosed with urothelial carcinoma. The median age of patients with paragangliomas of the bladder has been recorded as between 43 and 45 years[7, 11], compared to 70 years for patients with urothelial carcinoma.

Due to the comparative rarity of paragangliomas, their misdiagnosis cannot be avoided[12]. Uncontrolled hypertension during this kind of surgery should raise the suspicion of a paraganglioma. The operation should be suspended, radial artery and central venous cannulation should be performed and antihypertensive agents, such as nicardipine and sodium nitroprusside, in addition to antihypotensive diagents, such as norepinephrine, and β-blockers such as esmolol, should be prepared. A pathologist should be urgently consulted to confirm the diagnosis and the operation should be cancelled, if necessary.

CONCLUSION

Paragangliomas of urinary bladder are uncommon and often misdiagnosed especially when patients have no obvious hypertension. Due to the very high mortality rate without sufficient preparation preoperatively, uncontrolled hypertension during this kind of surgery should raise the suspicion of a paraganglioma and further preparation should be done.

ACKNOWLEDGEMENT

We thank Medjaden Bioscience Limited for assisting in the preparation of this manuscript

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2016; 48 (2) : 166 - 169

Epidermal Growth Factor Receptor Mutations in Nonsmall Cell Lung Carcinoma Patients in Kuwait

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J Cytol 2016; 33:1-6. doi: 10.4103/0970-9371.175476

Context: Nonsmall cell lung carcinoma (NSCLC) is the most frequently diagnosed form of lung cancer in Kuwait. NSCLC samples from Kuwait have never been screened for epidermal growth factor receptor (EGFR) gene aberration, which is known to affect treatment options.
Aims: This study investigated the feasibility of using fine-needle aspiration (FNA) material for mutational screening, and whether common EGFR mutations are present in NSCLC samples from Kuwait.
Settings and design: Eighteen NSCLC samples from five Kuwaitis and 13 non-Kuwaitis were included in this study.
Materials and methods: DNA was extracted from FNA cell blocks and screened for EGFR gene mutations using peptide nucleic acid (PNA)-clamp assay, and EGFR gene amplification using fluorescent in situ hybridization (EGFR-FISH). EGFR protein expression was assessed using immunohistochemistry.
Results: Five EGFR mutations were detected in five non-Kuwaiti NSCLC patients (27.8%). EGFR gene amplification was evident in 10 samples (55.5%) by direct amplification or under the influence of chromosomal polysomy. Four samples had EGFR mutations and EGFR gene amplification, out of which only one sample had coexisting EGFR overexpression.
Conclusions: Given the evidence of EGFR gene alterations occurring in NSCLC patients in Kuwait, there is a need to incorporate EGFR gene mutational screen for NSCLC patients to implement its consequent use in patient treatment.

Sinopulmonary Complications in Subjects with Primary Immunodeficiency

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Respir Care 2016 Mar 8. pii: respcare.04479. [Epub ahead of print]

Background: The aim of this work was to describe the frequency and spectrum of sinopulmonary complications among subjects with primary immunodeficiency disorders.
Methods: The subjects included all patients with primary immunodeficiency who were registered prospectively between January 2004 and December 2013 in the Kuwait National Primary Immunodeficiency Disorders Registry.

Results: A total of 202 subjects were registered during the study period. Subjects with combined immunodeficiencies were the most prevalent (65 subjects, 32.1%), followed by well-defined syndromes with immunodeficiency (45 subjects, 22.2%) and predominantly antibody deficiencies (35 subjects, 17.3%). A total of 295 sinopulmonary manifestations were observed in 127 subjects (63%); 157 manifestations (53.2%) were observed among the presenting symptoms, and 138 manifestations (46.8%) occurred after establishment of the primary immunodeficiency disorder diagnosis. Sinopulmonary manifestations were more common in subjects with predominantly antibody deficiencies (2.3 manifestations/subject), followed by subjects with combined immunodeficiencies (1.75 manifestations/subject). Pneumonia was the most common manifestation (108 episodes affecting 80 subjects), followed by otitis media (81 episodes affecting 59 subjects), bronchiectasis in 28 subjects (13.8%), and asthma in 22 subjects (11%). Microbial organisms were isolated during 46 episodes of pneumonia (42.5%) (cytomegalovirus and Pneumocystis jirovecii were the most common). There were 57 deaths (28%) during the study period. Twenty-four deaths (42%) were due to pulmonary complications as follows: pneumonia (16 subjects, 8%), pulmonary hemorrhage (6 subjects, 3%), and aspiration pneumonia (2 subjects, 1%).
Conclusions: Sinopulmonary complications are common in subjects with primary immunodeficiency. They can be serious and continue to occur even after proper treatment is initiated. The pulmonologist should play an important role in the management of subjects with primary immunodeficiency disorder.

Quadruple Therapy Versus Standard Triple Therapy for Eradication of Helicobacter Pylori in Kuwait

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Arab J Gastroenterol 2015; 16:131-5. doi: 10.1016/j.ajg.2015.09.007

Background and study aims: Chronic infection caused by Helicobacter pylori (H. pylori) is associated with chronic gastritis, peptic ulcer disease, and gastric cancer. Eradication of H. pylori reduces morbidity of chronic gastritis and incidence of gastric cancer in high-risk population. We aimed at testing the efficacy of clarithromycin-based triple therapy and bismuth-based quadruple therapy for eradicating H. pylori in patients with chronic gastritis in Kuwait.
Patients and methods: A total of 218 dyspeptic patients from different countries who were proved to have chronic gastritis by endoscopy and gastric biopsy were enroled. All of them were naïve to H. pylori eradication therapy. They were randomised into two groups: group A, received triple therapy (omeprazole, amoxicillin, and clarithromycin) for 10days; and group B, received quadruple therapy (omeprazole, bismuth subcitrate potassium, tetracycline, and metronidazole) for 10days. All patients were tested for eradication of H. pylori by carbon-13 urea breath test 4 weeks after treatment.
Results: Total response rate of eradication therapy in both groups was 77.5% (n = 169). However, group B (n = 100) had a higher eradication rate (88%) than group A (n = 118) (68.6%). H. pylori eradication rate was significantly higher in males (84.2%) than females (70.2%) in both groups ($p < 0.01$). There were no differences in eradication rates with regard to median age or nationality.
Conclusion: Bismuth-based quadruple therapy is more effective as a first-line therapy than clarithromycin-based triple therapy for eradicating H. pylori in patients with H. pylori-related chronic gastritis in Kuwait.

Validation of the Close-to-Delivery Prediction Model for Vaginal Birth after Cesarean Delivery in a Middle Eastern Cohort

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Int J Gynaecol Obstet 2016 Apr 1. pii: S0020-7292(16)30052-2. doi:10.1016/j.ijgo.2015.11.021. [Epub ahead of print]

Objective: To validate a prediction model for vaginal birth after cesarean (VBAC) that incorporates variables available at admission for delivery among Middle Eastern women.
Methods: The present prospective cohort study enrolled women at 37weeks of pregnancy or more with cephalic presentation who were willing to attempt a trial of labor (TOL) after a single prior low transverse cesarean delivery at Al-Jahra Hospital, Kuwait, between June 2013 and June 2014. The predicted success rate of VBAC determined via the close-to-delivery prediction model of Grobman et al. was compared between participants whose TOL was and was not successful.
Results: Among 203 enrolled women, 140 (69.0%) had successful VBAC. The predicted VBAC success rate was higher among women with successful TOL (82.4% ± 13.1%) than among those with failed TOL (67.7% ± 18.3%; P <0.001). There was a high positive correlation between actual and predicted success rates. For deciles of predicted success rate increasing from >30% - 40% to > 90% - 100%, the actual success rate was 20%, 30.7%, 38.5%, 59.1%, 71.4%, 76%, and 84.5%, respectively (r = 0.98, P = 0.013).
Conclusion: The close-to-delivery prediction model was found to be applicable to Middle Eastern women and might predict VBAC success rates, thereby decreasing morbidities associated with failed TOL.

Timing and Outcome of Referral to the First Stand-Alone Palliative Care Center in the Eastern Mediterranean Region, the Palliative Care Center of Kuwait

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Am J Hosp Palliat Care 2016 Jan 13. pii: 1049909115625959. [Epub ahead of print]

Background: Compared to other regions of the world, palliative care (PC) in the Eastern Mediterranean region is at an earlier stage of development. The Palliative Care Center of Kuwait (PCC-K) was established a few years ago as the first stand-alone PC center in the region. This study was conducted to investigate the timing of referral to the PCC-K and its outcome.
Methods: Retrospective review of referrals to the PCC-K during its first 3 years of action. Late referral was defined as referral during the last 30 days of life.
Results: During the 3-year period, 498 patients with cancer were referred to the PCC-K of whom 467 were eligible for analysis. Referral was considered late in 58% of patients. Nononcology facilities were more likely to refer patients late when compared to oncology facilities (P = .033). The palliative performance scale (PPS) was ≤30 in 59% of late referrals and 21% in earlier referrals (P < .001). Among 467 referred patients, 342 (73%) were eligible for transfer to the PCC-K, 102 (22%) were ineligible, and

23 (5%) died before assessment by the PCC-K consultation team. From the 342 eligible patients, the family caregivers refused the transfer of 64 (19%) patients to the PCC-K.
Conclusion: Patients are frequently referred late to the PCC-K. Further research to identify barriers to PC and its early integration in Kuwait is required. The PPS may be useful in identifying late referrals.

Consensus Recommendations for the Diagnosis and Treatment of Multiple Sclerosis in Kuwait

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Clin Neurol Neurosurg 201; 143:51-64. doi: 10.1016/j.clineuro.2016.02.001

Objectives: We aim to develop consensus recommendations to guide neurologists in the community for the diagnosis and treatment of Multiple Sclerosis (MS).
Methods: After reviewing the available literature, a group of neurologists with expertise in MS met to discuss the evidence and develop consensus recommendations for the diagnosis and treatment of MS.
Results: The revised 2010 McDonald criteria is the established diagnostic criteria for MS and has wide international acceptance among international MS experts. Several red flags in the history and examination, along with certain laboratory tests were pointed out to exclude MS mimickers in the diagnostic phase. The available approved disease modifying therapies (DMTs) were listed in an algorithmic fashion based on initial assessment of disease severity and subsequent disease breakthrough while on DMTs. Risk stratification based on the benefit versus risk ratio was used to help choosing the appropriate therapy to MS patients using an "individualized therapy" approach. The requirements for initiation and monitoring of treated MS patients were highlighted with emphasis on early identification of disease breakthrough, adverse events, and safety concerns. The role of multi-disciplinary MS clinics was discussed and a guide for referral to specialized MS clinics was developed.
Conclusions: Consensus recommendations have been developed to guide local neurologists on the diagnosis and treatment of patients with MS. Implementation of the revised 2010 McDonald diagnostic criteria was advised while a personalized treatment approach was recommended using a treatment algorithm based on risk stratification and patient-centered outcomes.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2016; 48 (2) : 170 - 181

2016 World Congress of **Cardiology & Cardiovascular** Health
Jun 4 - 7, 2016
Mexico / Mexico City
Contact: Mci Suisse Sa
Phone: 011-41-22-339-9585; Fax: 011-41-22-339-9631
Email: wcc2016reg@mci-group.com

10th International Conference on **Cholesteatoma & Middle Ear Surgery**
Jun 5 - 8, 2016
United Kingdom / Edinburgh
Contact: Matthew Yung, British Society Of Otology
Phone: 011-44-20-7808-5621
Email: chole2016@tfigroup.com

8th World Congress on **Pediatric Intensive & Critical** Care
Jun 5 - 8, 2016
Canada / Ontario / Toronto
Contact: Rebecca Johnstone, Kenes International
Phone: 011-41-22-908-0488
Email: picc@kenes.com

Global **Cancer: Occurrence, Causes** & Avenues to Prevention
Jun 7 - 10, 2016
France / Lyon
Contact: Conference Administrator, International Agency For Research On Cancer
Phone: 011-33-4-7273-8485
Email: iarc-conference2016@iarc.fr

Menopause Special Skills Module
Jun 9 - 10, 2016
United Kingdom / Gatwick
Contact: Kate Ellis, British Menopause Society
Phone: 011-44-16-2889-0199
Email: kate.ellis@bms-whc.org.uk

2016 **Transcatheter Valve** Therapies
Jun 16 - 18, 2016
United States / Illinois / Chicago
Contact: Center for Education, Cardiovascular Research Foundation
Phone: 646-434-4500
Email: cvi.markhartnett@verizon.net

10th International Symposium on **Pneumococci & Pneumococcal** Diseases
Jun 26 - 30, 2016
United Kingdom / Glasgow
Contact: Yoav Shlezinger, Kenes Group
Email: isppd@kenes.com

Medical CBT: Ten-Minute Techniques for Real Doctors (Cognitive Behaviour Therapy)
Jun 29 - Jul 1, 2016
Canada / Ontario / Collingwood
Contact: Greg Dubord, Md, Cme Director, Cbt Canada
Phone: 877-466-8228
Email: registrar@cbt.ca

7th International Workshop on Advances in the **Molecular Pharmacology & Therapeutics** of Bone & Other Musculoskeletal Diseases
Jul 2 - 6, 2016
United Kingdom / Oxford
Contact: Janet Crompton, Oxford Molpharm Workshop
Phone: 011-44-14-5354-9929; Fax: 011-44-14-5354-8919
Email: events@janet-crompton.com

2016 Symposium **Mammographicum**
Jul 3 - 5, 2016
United Kingdom / Liverpool
Contact: The Conference Collective Ltd
Phone: 011-44-20-8977-7997
Email: sympmamm@conferencecollective.co.uk

30th International College of **Neuropsychopharmacology** (CINP) World Congress
Jul 3 - 7, 2016
South Korea / Seoul
Contact: Cinp Central Office
Phone: 011-44-13-5524-4930; Fax: 011-44-13-5524-9959

14th International Congress of **Neuromuscular Diseases**
Jul 4 - 9, 2016
Canada / Ontario / Toronto
Contact: Dr. Vera Bril, Congress President
Phone: 604-566-8312; Fax: 604-681-1049
Email: icnmd2016@icsevents.com

9th **Ultrasound** for Intensive Care
Jul 4 - 5, 2016
United Kingdom / London
Contact: Infomed Research & Training
Phone: 011-44-20-3236-0810
Fax: 011-44-20-8290-6917
Email: courses@Infomedltd.co.uk

96th Annual British Association of **Dermatologists** (BAD) Meeting
Jul 5 - 7, 2016
United Kingdom / Birmingham, Uk
Contact: Conference & Event Services, Bad
Phone: 011-44-20-7391-6343
Fax: 011-44-20-7388-0487
Email: conference@bad.org.uk

9th Oswestry Shoulder & Elbow Course for **Orthopaedic** Trainees
Jul 6 - 7, 2016
United Kingdom / Oswestry
Contact: Orthopaedic Institute
Phone: 011-44-16-9140-4661
Email: enquiries@orthopaedic-institute.org

2nd Australasian **Breast** Congress
Jul 7 - 10, 2016
New Zealand / Auckland
Contact: Kerry Eyles, Executive Officer, Australasian Society for Breast Disease
Phone: 011-61-4-7733-0054
Email: kerrye@asbd.org.au

2016 Frontiers in **Cardiovascular Biology**
Jul 8 - 10, 2016
Italy / Florence
Contact: Council on Basic Cardiovascular Science
Phone: 011-33-4-9294-7600
Fax: 011-33-4-9294-7601

Hot Topics in **Infection & Immunity i**n Children
Jul 11 - 13, 2016
United Kingdom / London
Contact: Department Of Paediatrics, University Of Oxford
Phone: 011-44-18-6585-7466
Email: iic@paediatrics.ox.ac.uk

18th Annual International Society for **Bipolar Disorders** Conference / 8th Biennial International Society for Affective Disorders Conference
Jul 13 - 16, 2016
Netherlands / Amsterdam
Contact: Yoav Shlezinger, Kenes Group
Email: isbd2016@kenes.com

19th International Society for **Medical Shockwave** Treatment (ISMT) International Congress
Jul 14 - 16, 2016
Malaysia / Sarawak
Contact: Ismst
Phone: 011-43-732-302-373; Fax: 011-43-732-303-375
Email: shockwave@ismst.com

Seizures, Spells & Shakes: **Neurology** for the non-neurologist
Jul 14 - 16, 2016
Kiawah Island / South Carolina
Contact: Augusta University
Phone: 800-221-6437 or 706-721-3967
Fax: 706-721-4642
Email: coned@gru.edu

2nd International **Neonatology** association conference
Jul 15 - 17, 2016
Austria / Vienna
Contact: Sarah Krein, Paragon Group
Phone: 011-41-22-533-0948
Email: skrein@paragong.com

2nd Singapore **Cardiovascular** clinical trialists forum
Jul 15 - 17, 2016
Singapore / Singapore
Contact: Secretariat, CVCT Asia Forum
Email: secretariat@cvctasia.com

2016 International Conference on **Memory**
Jul 17 – 22, 2016
Hungary / Budapest
Contact: Organizing Secretariat, Asszisztencia Szervezo Kft.
Phone: 011-36-1-350-1854; Fax: 011-36-1-350-0929
Email: info@icom2016.com

Symposia at Sea: **Musculoskeletal Imaging** with MR
Jul 17 - 28, 2016
Denmark / Copenhagen
Contact: Educational Symposia
Phone: 800-338-5901 Or 813-806-1000
Fax: 800-344-0668 Or 813-806-1001

Focused point of care **Echocardiography**
Jul 18 - 20, 2016
United States / Florida / St. Pete Beach
Contact: Gulfcoast Ultrasound Institute
Phone: 800-619-1900 or 727-363-4500
Fax: 727-363-0811

Symposia at sea: **Head & Neck Imaging** - what you need to know
Jul 19 – 31, 2016
United Kingdom / Southampton
Contact: Educational Symposia
Phone: 800-338-5901 or 813-806-1000
Fax: 800-344-0668 or 813-806-1001

2016 American **Orthopaedic Foot & Ankle** Society (AOFAS) annual meeting
Jul 20 - 23, 2016
Canada / Ontario / Toronto
Contact: Aofas
Phone: 800-235-4855 or 847-698-4654 (Outside Us)
Email: aofasinfo@aofas.org

14th **Urological** Association of Asia Congress
Jul 21- 24, 2016
Singapore / Singapore
Contact: Congress Secretariat, Singapore Urological Association
Phone: 011-65-6513-7310
Email: uaa2016@globewerks.com

2016 **Neurooncology**
Jul 21 - 23, 2016
Australia / Brisbane
Contact: Rebecca Lynn, Omics International
Email: neurooncology@conferenceseries.com

2016 World Federation of **Hemophilia** (WFH) world congress
Jul 24 - 28, 2016
United States / Florida / Orlando
Contact: Wfh
Phone: 514-875-7944; Fax: 514-875-8916
Email: wfh@wfh.org

Comprehensive **Colposcopy**
Jul 27 - 30, 2016
United States/ Rhode Island
Contact: American Society for Colposcopy & Cervical Pathology
Phone: 800-787-7227 or 301-733-3640
Fax: 240-575-9880

International Conference on **Tumor Immunology and Immunotherapy**
Jul 28 - 30, 2016
Australia / Melbourne
Contact: Jennifer Jones, Program Manager, Omics International
Phone: 650-268-9744
Email: tumorimmunology@conferenceseries.com

24th **Swan Trauma** Conference
Jul 29 - 30, 2016
Australia / Sydney
Contact: Sonia Gagliardi, Swan Secretariat, Liverpool Hospital Trauma Department
Phone: 011-61-2-8738-3928; Fax: 011-61-2-8738-3926
Email: swan@sswahs.nsw.gov.au

Current Topics in **Emergency Medicine** - Paris
August 1- 5, 2016
France / Paris
Contact: Coleen Hilliard, Meeting Coordinator, Northwest Seminars
Phone: 509-547-7065; Fax: 509-547-1265
Email: info@northwestseminars.com

9th World **Cardiology** congress
Aug 1 - 3, 2016
United Kingdom / Manchester
Contact: Mercy Jyoshna, Program Co-ordinator, OMICS International Conferences
Phone: 702-508-5200 ext. 8033
Email: worldcardiology@conferenceseries.com

10th Asian Society of **Cardiovascular Imaging** (ASCI) congress
Aug 4 - 6, 2016
Singapore / Singapore
Contact: Qiuyi Seah (Ms), Asci 2016 Secretariat, The Meeting Lab Pte Ltd
Phone: 011-65-6346-4402; Fax: 011-65-6346-4403
Email: secretariat@asci2016.com

2016 **Stem Cell** Congress
Aug 4 - 5, 2016
United Kingdom / Manchester
Contact: Angelica, Stem Cell Congress, Omics International
Email: stemcellcongress@insightconferences.com

Advances In **Pulmonary Hypertension**
Aug 5, 2016
United States / Illinois / Chicago
Contact: Office of the CME, Feinberg School of Medicine, Northwestern University
Phone: 312-503-8533

40th Annual **Human Genetics** Society of Australasia Scientific Meeting
Aug 6 - 9, 2016
Australia / Hobart
Contact: Lisa King, Events Manager, AACB Services Pty Ltd
Phone: 011-61-2-9669-6600
Email: lisa@aacb.asn.au

Stoller: **Musculoskeletal Imaging** Tutorial & Mini-Fellowship
Aug 12 - 15, 2016
Australia / Melbourne
Contact: Administrator, Cme Science
Phone: 650-440-4424
Email: info@cmescience.com

46th **Orthopaedic Research Society** (ORS)
International Sun Valley Workshop: Musculoskeletal Biology
Aug 7 – 10, 2016
United States / Idaho / Sun Valley
Contact: ORS
Phone: 847-823-5770; Fax: 847-823-5772
Email: ors@ors.org

MR Spectroscopy: From current best practice to latest frontiers
Aug 14 - 17, 2016
Germany / Lake Constanz
Contact: International Society for Magnetic Resonance in Medicine
Email: info@ismrm.org

5th International African **Palliative Care** Conference
Aug 16 - 19, 2016
Uganda / Kampala
Contact: Patricia Batanda, African Palliative Care Association
Email: conference2016@africanpalliativecare.org

28th International Congress of **Pediatrics**
Aug 17 - 22, 2016
Canada / British Columbia
Contact: Congress Secretariat, MCI Group Canada Inc.
Phone: 604-688-9655 ext. 2; Fax: 604-685-3521
Email: info@IPA2016.com

15th Asian Oceanian Congress of **Neurology**
Aug 18 - 21, 2016
Malaysia / Kuala Lumpur
Contact: Congress, Secretariat, Kenes Asia
Phone: 011-65-6292-0723
Email: aocn2016@kenes.com

9th Latin American Congress on **Epilepsy**
Aug 20 - 23, 2016
Mexico / Cancun
Contact: Congress Secretariat
Phone: 011-353-1-205-6720; Fax: 011-353-1-205-6156

2016 International Congress of **Immunology**
Aug 21- 26, 2016
Australia / Melbourne
Contact: Congress Managers, Arinex Pty Ltd
Phone: 011-61-3-9417-0888; Fax: 011-61-3-9417-0899
Email: ici2016@arinex.com.au

2016 **Pediatric & Adult Congenital Cardiology** review course
Aug 21- 26, 2016
United States / California / Dana Point
Contact: Kimberly Feils, Mayo Clinic
Phone: 507-266-0676
Email: feils.kimberly@mayo.edu

28th Conference of European Comparative **Endocrinologists**
Aug 21 - 25, 2016
Belgium / Leuven
Contact: Prof. Dr. Med. Horst-Werner Korf, President, European Society for Comparative Endocrinology
Phone: 011-69-6-301-6040
Email: Korf@em.uni-frankfurt.de

30th World Congress of the International Association of **Logopedics & Phoniatrics**
Aug 21- 25, 2016
Ireland / Dublin
Contact: Mary-Rose Rushe, Keynote Pco
Email: info@ialpdublin2016.org

33rd World Congress of **Internal Medicine**
Aug 22 - 25, 2016
Indonesia / Bali
Contact: Conference Organizer, MCO® (Medical Conference Organizer)
Phone: 011-62-21-6386-9502
Fax: 011-62-21-6386-9503 / 05
Email: wcim2016@pharma-pro.com

28th International course on **Endoscopic Surgery** of the paranasal sinuses & skull base
Aug 24 - 27, 2016
Belgium / Ghent
Contact: Semico N.V.
Fax: 011-32-9-233-8597
Email: fess@semico.be

Advanced MR imaging in **Paediatric Radiology**
Aug 25 - 27, 2016
United Kingdom / London
Contact: Ms. Elena Skocek, Coordinator of Educational Activities & Congress Management, European Society for Magnetic Resonance in Medicine & Biology
Phone: 011-43-1-535-1306; Fax: 011-43-1-535-7041
Email: eskocek@esmrmb.org

Internal Derangements of Joints
Aug 25 - 28, 2016
Australia / Sydney
Contact: International Institute for Continuing Medical Education
Phone: 205-467-0290
Email: IICMEmail@gmail.com

2016 European Society for **Medical Oncology** (ESMO) Academy
Aug 26 - 28, 2016
United Kingdom / Oxford
Contact: Congress Department, ESMO
Phone: 011-41-91-973-1900; Fax: 011-41-91-973-1902
Email: esmo@esmo.org

21st International Summit on **Violence, Abuse & Trauma**
Aug 26 - 31st
United States / California / San Diego
Contact: Institute on Violence, Abuse & Trauma
Phone: 858-527-1860 ext. 4031; Fax: 858-527-1743
Email: ivat@alliant.edu

European **Molecular Biology** Laboratory (EMBL) conference: transcription & chromatin
Aug 27 - 30, 2016
Germany / Heidelberg
Contact: Course and Conference office, EMBL Heidelberg
Phone: 011-49-622-1387-8797
Email: events@embl.de

16th World Congress of **Anaesthesiologists**
Aug 28 - Sep 2, 2016
China / Hong Kong
Contact: Coralie Deleage, Mci Group
Email: coralie.deleage@mci-group.com

16th World Congress on **Cancers of the Skin** / 12th Congress of the European Association of Dermato-Oncology
Aug 31- Sep 3, 2016
Austria / Vienna
Contact: Mci Deutschland Gmbh
Phone: 011-49-30-204-590
Email: wccs2016@mci-group.com

17th Asia-Pacific **Prostate Cancer** Conference
Aug 31- Sep 3, 2016
Australia / Melbourne
Contact: Icms Pty Ltd
Phone: 011-61-1-3007-92466
Fax: 011-61-3-9818-7111
Email: apcc2014@icms.com.au

6th Oxford **Bone Infection** Conference
Aug 31, 2016
United Kingdom / Oxford
Contact: Hartley Taylor Medical Communications
Phone: 011-44-15-6562-1967
Email: office@hartleytaylor.co.uk

19th **Liver Imaging** workshop
Sep 1- 2, 2016
Malta / St. Julian's
Contact: Central European Society of Gastrointestinal & Abdominal Radiology office
Phone: 011-43-1-535-8927
Fax: 011-43-1-535-8927 Ext. 15
Email: office@esgar.org

35th Annual European **Bone & Joint Infection** Society meeting
Sep 1- 3, 2016
United Kingdom / Oxford
Contact: Hartley Taylor Medical Communications
Phone: 011-44-15-6562-1967
Email: office@hartleytaylor.co.uk

Advanced **Cardiac MR** Imaging
Sep 1- 3, 2016
Croatia / Zagreb
Contact: Ms. Elena Skocek, Coordinator of Educational Activities & Congress Management, European Society For Magnetic Resonance In Medicine & Biology
Phone: 011-43-1-535-1306; Fax: 011-43-1-535-7041
Email: eskocek@esmrmb.org

Hot Topic Conference: Life Course Influences & Mechanisms: **Obesity, Physical Activity & Cancer**
Sep 1 – 2, 2016
United Kingdom / London
Contact: World Obesity Federation
Email: hottopics@worldobesity.org

Central Nervous System MRI II
Sep 2- 6, 2016
United Kingdom / Sheffield
Contact: Walter Rijsselaere, Erasmus MRI Course
Email: walter.rijsselaere@uzbrussel.be

39th European **Thyroid** Association (ETA) Annual Meeting
Sep 3- 7, 2016
Denmark / Copenhagen
Contact: Eta Standing Office
Phone: 011-49-61-3676-2197
Fax: 011-49-61-3676-1953
Email: euro-thyroid-assoc@endoscience.de

16th European congress of **Neurosurgery**
Sep 4 - 8, 2016
Greece / Athens
Contact: Amy Pinchbeck Smith, European Association of Neurosurgical Societies
Email: amy.pinchbecksmith@eans.org

2016 Status quo of **Brain Infections**
Sep 4 - 7, 2016
Turkey / Izmir
Contact: Thomas Greif, Education Manager, European Society of Clinical Microbiology & Infectious Diseases
Phone: 011-41-61-508-0153
Fax: 011-41-61-508-0151
Email: info@escmid.org

20th International **Pathogenic Neisseria** conference
Sep 4 - 9, 2016
United Kingdom / Manchester
Contact: Hartley Taylor Medical Communications
Phone: 011-44-15-6562-1967
Email: kristy@hartleytaylor.co.uk

6th International Course in **Nutritional Epidemiology**
Sep 5 - 16, 2016
United Kingdom / London
Contact: Centre For Continuing Professional Development, Imperial College London
Phone: 011-44-20-7594-6881
Fax: 011-44-20-7594-6883
Email: cpd@imperial.ac.uk

46th Annual European Society for **Dermatological Research** (ESDR) Meeting
Sep 6 - 10, 2016
Germany / Munich
Contact: ESDR
Phone: 011-41-22-321-4890
Email: office@esdr.org

5th International symposium on **Hepatitis Care** in substance users
Sep 7 - 9, 2016
Norway / Oslo
Contact: Conference Sectretariat, ASHM Conference & Events Division
Phone: 011-61-2-8204-0770; Fax: 011-61-2-8204-0779
Email: info@inhsu2016.com

16th **Euretina** congress
Sep 8 - 11, 2016
Denmark / Copenhagen
Contact: Euretina
Phone: 011-353-1-210-0092; Fax: 011-353-1-209-1112
Email: euretina@euretina.org

2016 European Society of **Gynaecological Oncology** (ESGO) State of the art Gynaecological Oncology conference
Sep 8 - 10, 2016
Turkey / Antalya
Contact: Lucie Lamlova, Esgo
Email: lucie.lamlova@esgomail.org

2nd World Congress on Controversies in **Breast Cancer**
Sep 8 - 11, 2016
Spain / Barcelona
Contact: Ilana Rabinoff-Sofer, Congressmed
Phone: 011-972-73-706-6954
Email: cobrca@congressmed.com

1st Asia Pacific **Diabetes, Hypertension, Metabolic Syndrome & Pregnancy** Symposium: maternal medicine meets fetal medicine
Sep 8 - 10, 2016
Sri Lanka / Colombo
Contact: ComtecMed, ComtedMed
Email: dipap-saidip@comtecmed.com

Eastern Europe & Balkan Region Refresher Course on **Gastro-Intestinal Cancer**
Sep 8 - 9, 2016
Hungary / Budapest
Contact: European School of Oncology
Phone: 011-39-2-854-6451; Fax: 011-39-2-8546-4545
Email: eso@eso.net

2nd World Congress on Controversies in **Breast Cancer**
Sep 8 - 11, 2016
Spain / Barcelona
Contact: Ilana Rabinoff-Sofer, CongressMed
Phone: 011-972-73-706-6954
Email: cobrca@congressmed.com

Galen Advanced course on **Paediatric** imaging
Sep 8 - 9, 2016
France / Paris
Contact: European School of Radiology
Phone: 011-43-1-533-4064; Fax: 011-43-1-533-4064 Ext. 447

13th **Diabetic Foot** Study Group (DFSG) meeting
Sep 9 - 11, 2016
Germany / Stuttgart
Contact: Dfsg Meeting Secretariat, Cap Partner
Phone: 011-45-7020-0305
Email: dfsg@dfsg.org

5th International Congress on **Lipid Metabolism & Atherosclerosis**
Sep 9 - 10, 2016
South Korea / Seoul
Contact: Jung Mi OH, Team Leader, HENS MICE Solution
Phone: 011-82-2-2616-0927
Fax: 011-82-2-704-0928
Email: jmoh@hensmice.com

Parkinson's Disease: beyond tremor
Sep 9, 2016
United States / New York / New York
Contact: Maria Mercado, Registrar, New York University School of Medicine
Phone: 212-263-5295; Fax: 212-263-5293
Email: maria.mercado@nyumc.org

Intensive Care **Clinical Microbiology & Infectious Disease** Course
Sep 10 - 11, 2016
India / New Delhi
Contact: Dr Yash Javeri, Course director, Indian Society of Critical Care Medicine Delhi NCR
Phone: 011-91-981-871-6943
Email: isccmdelhichapter@gmail.com

12th European Congress on **Epileptology**
Sep 11 - 15, 2016
Czech Republic / Prague
Contact: Congress Secretariat
Phone: 011-353-1-205-6720

2016 **Interdisciplinary Endovascular Aortic** Symposium (IDEAS)
Sep 11 - 13, 2016
Spain / Barcelona
Contact: Ms. Verena Wagner-Rath, Congress & Conference Management, Cirse Congress Research Education Gmbh
Phone: 011-43-1-904-2003; Fax: 011-43-1-904-2003 Ext. 30
Email: info@cirse.org

18th International workshop on co-morbidities & adverse drug reactions in **HIV**
Sep 12 - 13, 2016
United States / New York / New York
Contact: Organizing Secretariat, International Medical Press
Phone: 011-44-20-7398-0700; Fax: 011-44-20-7398-0701
Email: comorbidities@nucleuscentral.com

23rd European Association for **Cranio Maxillofacial Surgery** congress
Sep 13 - 16, 2016
United Kingdom / London
Contact: Yoav Shlezinger, Kenes Group
Phone: 011-41-22-906-9178; Fax: 011-41-22-732-2607
Email: eacmfs2016@kenes.com

21st International Congress on **Palliative Care**
Sep 13 - 16, 2016
Canada / Quebec / Montreal
Contact: Congress Secretariat, O'Donoughue & Associates event management
Phone: 450-292-3456 ext. 227; Fax: 450-292-3453
Email: secretariat@pal2014.com

46th Annual International **Continence** Society meeting
Sep 13 - 16, 2016
Japan / Tokyo
Contact: Josh Margo, Kenes International
Phone: 011-41-2-2908-0488
Email: jmargo@kenes.com

13th European Society of **Contact Dermatitis** congress
Sep 14 - 17, 2016
United Kingdom / Manchester
Contact: Conference & Event Services, British Association Of Dermatologists
Phone: 011-44-20-7391-6343; Fax: 011-44-20-7388-0487
Email: conference@bad.org.uk

19th Annual European Society for **Clinical Virology** meeting
Sep 14 - 17, 2016
Portugal / Lisbon
Contact: Dr. Svein Arne Nordbo, University Hospital Of Trondheim
Phone: 011-47-72-573-310
Email: svein.a.nordbo@ntnu.no

43rd Annual European Society for **Artificial Organs** (ESAO) Congress
Sep 14 - 17, 2016
Poland / Warsaw
Contact: Anita Aichinger, Center for Biomedical Technology Danube University-Krems, Esao Office
Phone: 011-43-2732-893–2633; Fax: 011-43-2732-893–4600
Email: anita.aichinger@donau-uni.ac.at

Proteomics in **Cell Biology & Disease** Mechanisms
Sep 14 - 17, 2016
Germany / Heidelberg
Contact: Course and Conference Office, European Molecular Biology Laboratory, EMBL Heidelberg
Phone: 011-49-622-1387-8797
Email: events@embl.de

2016 Mucosal Vaccines, **Adjuvants & Delivery**
Sep 14 - 16, 2016
Switzerland / Lausanne
Contact: Caroline Sumner, Meetings Management
Phone: 011-44-14-8342-7770; Fax: 011-44-14-8342-8516
Email: csumner@meetingsmgmt.u-net.com

2016 **Hypertension**
Sep 15 - 16, 2016
Thailand / Phuket
Contact: Dr Charles, IM Clinic
Email: info@nbscience.com

Targeted treatments for **Paediatric Cancers**
Sep 15, 2016
United Kingdom / London
Contact: Education and Conference Centre, The Royal Marsden NHS Foundation Trust
Phone: 011-44-20-7808-2921; Fax: 011-44-20-7808-2334
Email: conferencecentre@rmh.nhs.uk

2016 International Society of **Gynecological Endoscopy** / Indonesian Gynecological Endoscopy Society Asian Conference
Sep 15 - 17, 2016
Indonesia / Bali
Contact: Traveland Convex Indonesia
Phone: 011-62-22-426-4028; Fax: 011-62-22-426-4029
Email: mice@travelandconvex.com

30th International Union Against **Sexually Transmitted Infections**-Europe Conference
Sep 15 - 17, 2016
Hungary / Budapest
Contact: Zsombor Papp, General Manager, Convention Budapest Ltd.
Phone: 011-36-1-299-0184
Fax: 011-36-1-299-0187
Email: zspapp@convention.hu

17th International Conference on **Systems Biology**
Sep 16 - 20, 2016
Spain / Barcelona
Contact: Alejandro Hernandez, Kenes Group
Phone: 011-34-91-361-2600
Email: mediatks@kenes.com

4th **Aesthetic & Anti-Aging Medicine** World Congress Eastern Europe
Sep 16 - 17, 2016
Russia / Moscow
Contact: Euromedicom
Phone: 011-33-1-5683-7800; Fax: 011-33-1-5683-7805

9th Annual Perspectives in **Rheumatic Diseases** Conference
Sep 16 - 17, 2016
United States / Nevada / Las Vegas
Contact: Global Academy for Medical Education
Fax: 866-401-8609
Email: n.rillo@globalacademycme.com

Pan Europe **Pacific Medical & Legal** Conference
Sep 16 - 23 , 2016
Spain / Barcelona
Contact: Continuing Professional Education Pty Ltd
Phone: 011-61-7-3254-3331; Fax: 011-61-7-3254-3332
Email: conferences@educationcpe.com

19th International Congress for **Tropical Medicine & Malaria**
Sep 18 – 22, 2016
Australia / Brisbane
Contact: Arinex Pty Ltd
Phone: 011-61-2-9265-0700; Fax: 011-61-2-9267-5443
Email: tropicalmedicine2016@arinex.com.au

Advanced **ECG Interpretation** Boot Camp in Budapest, Hungary
Sep 19 – 22, 2016
Hungary / Budapest
Contact: Jerry W. Jones, Md Facep Faaem, Ceo And Principal Instructor, Medicus Of Houston
Phone: 713-931-5423; Fax: 888-308-7807
Email: jwjmd@medicusofhouston.com

2016 International Society for Diseases of the **Esophagus** World Congress
Sep 19 - 21, 2016
Singapore / Singapore
Contact: Congress Secretariat, International Conference Services, Ltd.
Phone: 604-681-2153; Fax: 604-681-1049
Email: isde2016@icsevents.com

17th International **Pediatric Nephrology** Association Congress
Sep 20 - 24, 2016
Brazil / Iguaçu
Contact: Europa Organisation
Phone: 011-33-5-607-0809; Fax: 011-33-5-607-0810
Email: ipna-registration@europa-organisation.com

4th World **Parkinson** Congress
Sep 20 - 23, 2016
United States/ Oregon / Portland
Contact: World Parkinson Coalition
Phone: 800-457-6676
Email: info@worldpdcongress.org

17th Biennial Meeting of The European Society for **Immunodeficiencies**
Sep 21- 24, 2016
Spain / Barcelona
Contact: Jennifer Simon, Kenes International
Phone: 011-41-22-908-0488
Email: esid@kenes.com

2016 Korean Congress of **Radiology**
Sep 21 - 24, 2016
South Korea / Seoul
Contact: Secretariat, In Session International Convention Services, Inc.
Phone: 011-82-2-3452-7199; Fax: 011-82-2-521-8683
Email: info@kcr4u.org

Cytoreductive Surgery for Ovarian Cancer & Peritoneal Surface Malignancies
Sep 21 - 22, 2016
United Kingdom / Newcastle
Contact: Lorraine Waugh, Newcastle Surgical Training Centre
Phone: 011-44-19-1223-1264; Fax: 011-44-19-1223-7248
Email: lorraine.waugh@nuth.nhs.uk

Minimally Invasive **Spine Surgery & Complex** Procedures Workshop
Sep 21 - 22, 2016
Indonesia / Surabaya
Contact: North American Spine Society
Phone: 866-960-6277 or 630-230-3600
Email: registration@spine.org

6th International Conference on **Clinical Neonatology**
Sep 22 - 24, 2016
Italy / Torino
Contact: Organizing Secretariat, MCA Scientific Events
Phone: 011-39-2-3493-4404
Email: massaro@mcascientificevents.eu

2016 Canadian **Fertility & Andrology** Society (CFAS) Annual Meeting
Sep 22- 24, 2016
Canada / Ontario / Toronto
Contact: Cfas National Office
Phone: 514-524-9009; Fax: 514-524-2163
Email: info@cfas.ca

6th International Conference on Clinical **Neonatology**
Sep 22- 24, 2016
Italy / Torino
Contact: Organizing Secretariat, Mca Scientific Events
Phone: 011-39-2-3493-4404
Email: massaro@mcascientificevents.eu

Vascular Interpretation & RPVI Review & Scanning Skills Workshop
Sep 22- 24, 2016
United States / Florida / St. Peters Beach
Contact: Gulfcoast Ultrasound Institute
Phone: 800-619-1900 Or 727-363-4500
Fax: 727-363-0811

13th International **Cartilage Repair** Society (ICRS) World Congress
Sep 24 - 27, 2016
Italy / Naples
Contact: Icrs
Phone: 011-41-44-503-7370; Fax: 011-41-44-503-7372
Email: office@cartilage.org

2016 World Union of **Wound Healing** Societies Congress
Sep 25 - 29, 2016
Italy / Florence
Contact: Congress Secretariat, Centro Congressi Internazionale Srl
Phone: 011-39-11-244-6911; Fax: 011-39-11-244-6950
Email: info@wuwhs2016.com

22nd Biennial Meeting of the International Society for **Eye Research** (ISER)
Sep 25 - 29, 2016
Japan / Tokyo
Contact: Meeting Secretariat, ISER
Phone: 011-49-3024-6030
Email: iser2016@kit-group.org

Infectious Diseases in pregnant women, fetuses & newborns
Sep 25 - 29, 2016
Italy / Bertinoro
Contact: Thomas Greif, Education Manager, European Society of Clinical Microbiology & Infectious Diseases
Phone: 011-41-61-508-0153; Fax: 011-41-61-508-0151
Email: info@escmid.org

Radiology in Portugal
Sep 25 - Oct 1, 2016
Portugal / Porto
Contact: Radiology Conference Team, Radiology International Inc.
Phone: 860-225-1700
Email: info@radiologyintl.com

26th World Congress on **Ultrasound in Obstetrics & Gynecology**
Sep 25 - 28, 2016
Italy / Rome
Contact: Congress Secretariat, International Society of Ultrasound in Obstetrics & Gynecology
Phone: 011-44-20-7471-9955; Fax: 011-44-20-7471-9959
Email: congress@isuog.org

18th Asia Pacific League of Associations for **Rheumatology** Congress
Sep 26 - 29, 2016
China / Shanghai
Contact: Suzanne Khoo, Kenes MP Asia
Phone: 011-65-6-292-0723
Email: skhoo@kenes.com

16th World Congress on **Pain**
Sep 26 - Oct 1, 2016
Japan / Yokohama
Contact: Congress Secretariat, MCI Tokyo
Phone: 011-81-3-3508-9031; Fax: 011-81-3-3508-2017
Email: iasp2016@mci-group.com

Anaerobic Bacteria: Next Generation Technology Meets **Anaerobic Diagnostics**
Sep 26 - 28, 2016
Netherlands / Groningen
Contact: Thomas Greif, Education Manager, European Society Of Clinical Microbiology & Infectious Diseases
Phone: 011-41-61-508-0153; Fax: 011-41-61-508-0151
Email: info@escmid.org

Body Diffusion-Weighted MRI: From theory to practice
Sep 26 - 28, 2016
Austria / Vienna
Contact: Ms. Elena Skocek, Coordinator of Educational Activities & Congress Management, European Society For Magnetic Resonance In Medicine & Biology
Phone: 011-43-1-535-1306; Fax: 011-43-1-535-7041
Email: eskocek@esmrmb.org

Musculoskeletal MRI (Comprehensive Course)
Sep 26 - 30, 2016
Greece / Heraklion
Contact: Mika Travel, Secretariat
Phone: 011-30-28-1022-3356
Email: congress@mikatravel.eu

11th Annual European Society of **Coloproctology** (ESCP) meeting
Sep 28 - 30, 2016
Turkey / Istanbul
Contact: Escp Secretariat, Integrity International Events Ltd.
Phone: 011-44-13-1624-6040; Fax: 011-44-13-1624-6045

15th World Congress on **Menopause**: Heart Health Matters
Sep 28 - Oct 1, 2016
Czech Republic / Prague
Contact: Ms Lee Tomkins, Executive Director, International Menopause Society
Phone: 011-44-120-971-1054; Fax: 011-44-120-961-0530
Email: leetomkinsims@btinternet.com

22nd Congress of the European Society for **Stereotactic & Functional Neurosurgery**
Sep 28 - Oct 1, 2016
Turkey / Istanbul
Contact: Organization Secretariat, Flap Tour
Phone: 011-90-312-454-0000; Fax: 011-90-312-454-0001
Email: essfn2016@flaptour.com.tr

15th World Congress on **Menopause**: Heart Health Matters
Sep 28 - Oct 1, 2016
Czech Republic / Prague
Contact: Ms Lee Tomkins, Executive Director, International Menopause Society
Phone: 011-44-120-971-1054; Fax: 011-44-120-961-0530
Email: leetomkinsims@btinternet.com

10th Australasian **Viral Hepatitis** Conference
Sep 29 - Oct 1, 2016
Australia / Gold Coast
Contact: Conference Secretariat, Ashm Conference And Events Division
Phone: 011-61-2-8204-0070; Fax: 011-61-2-9212-4670
Email: conference.mailbox@ashm.org.au

15th International Workshop on Multiple **Endocrine Neoplasia** & Other Rare Endocrine Tumors
Sep 29 - Oct 1, 2016
Netherlands / Utrecht
Contact: Congress By Design
Phone: 011-31-8-8089-8101
Email: worldmen2016@congressbydesign.com

2016 British Society for **Allergy & Clinical Immunology** (BSACI) Annual Meeting
Sep 29 - Oct 1, 2016
United Kingdom / Telford
Contact: Karen Anthony, Bsaci
Phone: 011-44-14-6247-6315
Email: bsaci@medivents.co.uk

34th World **Sports Medicine** Congress
Sep 29 - Oct 2, 2016
Turkey / Istanbul
Contact: Organizing Secretariat, Dekon Congress & Tourism
Phone: 011-90-212-347-6300; Fax: 011-90-212-347-6363
Email: secretariat@fims2016.com

15th International Workshop on **Multiple Endocrine Neoplasia** & other rare endocrine tumors
Sep 29 - Oct 1, 2016
Netherlands / Utrecht
Contact: Congress by design
Phone: 011-31-8-8089-8101
Email: worldmen2016@congressbydesign.com

8th International Conference on Clinical **Gastroenterology & Hepatology**
Sep 29 - Oct 1, 2016
Canada / Ontario / Toronto
Contact: Sandra J, Omics Grp
Phone: 650-268-9744
Email: clinicalgastroenterology@insightconferences.com

30th European Association for **Cardio-Thoracic Surgery** (EACTS) Annual Meeting
Oct 1- 5, 2016
Spain / Barcelona
Contact: Eacts House
Phone: 011-44-17-5383-2166; Fax: 011-44-17-5362-0407

16th International **Nutrition & Diagnostics** Conference
Oct 3 - 6, 2016
Czech Republic / Prague
Contact: Citlalli Garnica Ortiz, RADANAL Ltd.
Phone: 011-420-469-779-899; Fax: 011-420-467-027-020
Email: info@indc.cz

National **Head & Neck** Fellows Cadaveric Course
Oct 3 - 4, 2016
United Kingdom / Newcastle upon Tyne
Contact: Lorraine Waugh, Newcastle Surgical Training Centre
Phone: 011-44-19-1223-1264; Fax: 011-44-19-1223-7248
Email: lorraine.waugh@nuth.nhs.uk

5th World Congress of **Pediatric Gastroenterology, Hepatology & Nutrition**
Oct 5 - 8, 2016
Canada / Quebec / Montreal Gastroenterology
Contact: Meeting Organiser, CG & I
Phone: 514-846-9191; Fax: 514-846-9393

Colonoscopy & Endoscopy Course
Oct 5 - 7, 2016
United Kingdom / Newcastle Upon Tyne
Contact: Lorraine Waugh, Newcastle Surgical Training Centre
Phone: 011-44-19-1223-1264; Fax: 011-44-19-1223-7248
Email: lorraine.waugh@nuth.nhs.uk

3rd World Congress on **Hepatitis & Liver Diseases**
Oct 10 - 12, 2016
United Arab Emirates / Dubai
Contact: Joseph Raven, Mr, Omics International
Email: hepatitis@omicsgroup.com

29th International Course on **Therapeutic Endoscopy**
Oct 12 - 14, 2016
Canada /Ontario / Toronto
Contact: Therapeutic Endoscopy Group, St. Michael's Hospital
Phone: 416-864-5329; Fax: 416-864-5803
Email: therendo@interlog.com

9th Asia Pacific **Heart Rhythm Society** Scientific Session (APHRS 2016)
Oct 12 - 15, 2016
South Korea / Seoul
Contact: APHRS 2016 Secretariat
Email: aphrs2016@intercom.co.kr

2016 International Conference on **Autoimmunity**
Oct 13 - 15, 2016
United Kingdom / Manchester
Contact: Christi Brown, Program Coordinater, OMICS International
Phone: 800-216-6499; Fax: 650-618-1417
Email: autoimmunity@conferenceseries.com

8th International Society of **Vascular Behavioural & Cognitive Disorders** International Meeting: Vascog 2016
Oct 13 - 15, 2016
Netherlands / Amsterdam
Contact: VasCog 2016
Phone: 011-31-20-444-0816;
Email: info@vascog2016.nl

Deep Brain Stimulation for Movement Disorders
Oct 13 - 14, 2016
Germany / Wurzburg
Contact: International Secretariat, International Parkinson & Movement Disorder Society
Phone: 414-276-2145; Fax: 414-276-3349
Email: info@movementdisorders.org

Mena **Physical Medicine & Rehabilitation** congress
Oct 13 - 15, 2016
United Arab Emirates / Dubai
Contact: Ahmed Thabet, Marketing Manager, Maarefah Management
Phone: 011-971-4-361-9616
Email: info@menaphysicalrehab.com

Myoclonus & other jerky movements
Oct 13 - 14, 2016
Netherlands / Groningen
Contact: International Secretariat, International Parkinson & Movement Disorder Society
Phone: 414-276-2145; Fax: 414-276-3349
Email: info@movementdisorders.org

2016 Acute **Cardiovascular Care**
Oct 15 - 17, 2016
Portugal / Lisbon
Contact: Acute Cardiovascular Care Association
Phone: 011-33-4-9294-7600
Fax: 011-33-4-9294-7601

13th Global Summit on **Cancer Therapy**
Oct 17 - 19, 2016
United Arab Emirates / Dubai
Contact: Celina Crystal, OMICS International
Phone: 011-650-268-9744; Fax: 011-650-618-1414
Email: middleeastoncologists@conferenceseries.com

2016 Joint Congress of Asia Pacific Association of Allergy, **Asthma & Clinical Immunology** / Asia Pacific Association of Pediatric Allergy, Respirology & Immunology
Oct 17 - 20, 2016
Malaysia / Kuala Lumpur
Contact: Sue Wong, Congress Secretariat, Malaysian Society of Allergy & Immunology
Phone: 011-60-32-162-0566
Email: info@apaaaci-kl2016.org

18th International **Psycho Oncology** Society Congress
Oct 17 – 21, 2016
Ireland / Dublin
Contact: Valerie Abbott, Conference Secretariat
Phone: 011-353-1-648-6278
Email: Iposdublin2016@abbey.ie

48th Congress of the International Society of **Paediatric Oncology**
Oct 19 - 22, 2016
Ireland / Dublin
Contact: Secretariat, Kenes International
Phone: 011-41-22-906-9178
Email: siop@kenes.com

3rd Congress on Controversies In **Thrombosis & Hemostasis** / 8th Russian Conference on Clinical Hemostasiology & Hemorheology
Oct 20 - 22, 2016
Russia / Moscow
Contact: Secretariat, Secretariat, CongressMed
Phone: 011-41-22-339-9985
Email: cith@congressmed.com

4th World Congress on **Controversies, Debates & Consensus in Bone,** Muscle & Joint Diseases
Oct 20 - 22, 2016
Spain / Barcelona
Contact: Secretariat, CongressMed
Phone: 011-41-22-339-9985
Email: bmjd@congressmed.com

6th Clinical **Microbiology** Conference
Oct 20 – 22, 2016
Italy / Rome
Contact: Stephen Bruce, Mr., Omics International
Phone: 650-268-9744
Email: clinicalmicrobiology@conferenceseries.net

Cadaveric Laparoscopic Surgery Workshop in Gynaecological Oncology
Oct 20 – 21, 2016
United Kingdom / Newcastle Upon Tyne
Contact: Mr Ali Kucukmetin, Newcastle Surgical Training Centre
Email: ali.metin@ghnt.nhs.uk

Spinal Instructional Cadaveric Course
Oct 20 – 21, 2016
United Kingdom / Newcastle Upon Tyne
Contact: Richard Patterson
Email: rpatter1@ITS.JNJ.com

3rd World Congress of **Cutaneous Lymphomas**
Oct 26 - 28, 2016
United States / New York / New York
Contact: ColumbiaCME, Columbia University College of Physicians & Surgeons
Phone: 212-305-3334
Email: cme@columbia.edu

International Current Concepts for the SI Joint in **Spine Conditions & Surgical Techniques**
Oct 30, 2016
Singapore / Singapore
Contact: North American Spine Society
Phone: 866-960-6277 or 630-230-3600
Email: registration@spine.org

2016 International meeting on **Emerging Diseases & Surveillance**
Nov 4 - 7, 2016
Austria / Vienna
Contact: International Society for Infectious Diseases
Phone: 617-277-0551; Fax: 617-278-9113
Email: info@isid.org

7th International **Hip Arthroscopy** Meeting
Nov 4 - 5, 2016
Germany / Munich
Contact: Stefanie Matt, Project Manager Conventions, Intercongress Freiburg
Phone: 011-49-761-696-99243; Fax: 011-49-761-696-9911
Email: stefanie.matt@intercongress.de

Neuro/ENT in Hong Kong
Nov 4 - 6, 2016
China / Hong Kong
Contact: International Institute for Continuing Medical Education
Phone: 205-467-0290
Email: IICMEmail@gmail.com

3rd Singapore Advanced **Rhinoplasty Fresh Frozen Cadaveric Dissection** course
Nov 6 - 9, 2016
Singapore / Singapore
Contact: Secretariat, Course Secretariat, Khoo Teck Puat Hospital
Email: SingaporeENTcourses@barakpco.com

50th Annual Congress of Turkish **Ophthalmology** society
Nov 9 - 13, 2016
Turkey / Antalya
Contact: Ms. Nagihan Tunali, Project Coordinator, Global Turizm Organizasyon Inc.
Phone: 011-90-21-2282-9232
Email: todnet@globalturizm.com.tr

12th Hanover **Arthroscopy & Arthroplasty** course
Nov 11 - 12, 2016
Germany / Hanover
Contact: Congress Office, Intercongress GmbH
Phone: 011-49-611-977-160
Email: info.wiesbaden@intercongress.de

21st Congress of the Asian Pacific Society of **Respirology**
Nov 12 - 15, 2016
Thailand / Bangkok
Contact: Warapa Saipow, Kenes Asia (Thailand) Co., Ltd.
Phone: 011-66-2748-7881
Email: wsaipow@kenes.com

WHO-Facts Sheet

1. Poliomyelitis
2. Ageing and Health
3. Road Traffic Injuries
4. Antimicrobial Resistance
5. Dengue and Severe Dengue

Compiled and edited by
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1. POLIOMYELITIS

Overview

Poliomyelitis (polio) is a highly infectious viral disease, which mainly affects young children. The virus is transmitted by person-to-person spread mainly through the faecal-oral route or, less frequently, by a common vehicle (*e.g.* contaminated water or food**)** and multiplies in the intestine, from where it can invade the nervous system and can cause paralysis.

Initial symptoms of polio include fever, fatigue, headache, vomiting, stiffness in the neck, and pain in the limbs. In a small proportion of cases, the disease causes paralysis, which is often permanent. There is no cure for polio, it can only be prevented by immunization.

KEY FACTS

- Polio (poliomyelitis) mainly affects children under 5 years of age.
- 1 in 200 infections leads to irreversible paralysis. Among those paralysed, 5% to 10% die when their breathing muscles become immobilized.
- Polio cases have decreased by over 99% since 1988, from an estimated 350 000 cases then, to 74 reported cases in 2015. The reduction is the result of the global effort to eradicate the disease.
- Today, only 2 countries (Afghanistan and Pakistan) remain polio-endemic, down from more than 125 in 1988.
- As long as a single child remains infected, children in all countries are at risk of contracting polio. Failure to eradicate polio from these last remaining strongholds could result in as many as 200 000 new cases every year, within 10 years, all over the world.
- In most countries, the global effort has expanded capacities to tackle other infectious diseases by building effective surveillance and immunization systems.

Global caseload

Polio does still exist, although polio cases have decreased by over 99% since 1988, from an estimated more than 350,000 cases to 359 reported cases in 2014. This reduction is the result of the global effort to eradicate the disease. Today, only two countries in the world have never stopped transmission of polio (Pakistan and Afghanistan).

Of the 3 strains of wild poliovirus (type 1, type 2, and type 3), wild poliovirus type 2 was eradicated in 1999 and case numbers of wild poliovirus type 3 are down to the lowest-ever levels with the no cases reported since a case reported by Nigeria in November 2012.

Despite the progress achieved since 1988, as long as a single child remains infected with poliovirus, children in all countries are at risk of contracting the disease. The poliovirus can easily be imported into a polio-free country and can spread rapidly amongst unimmunized populations. Failure to eradicate polio could result in as many as 200,000 new cases every year, within 10 years, all over the world.

There is no cure for polio, it can only be prevented. Polio vaccine, given multiple times, can protect a child for life.

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Polio and its symptoms

Polio is a highly infectious disease caused by a virus. It invades the nervous system, and can cause total paralysis in a matter of hours. The virus is transmitted by person-to-person spread mainly through the faecal-oral route or, less frequently, by a common vehicle (for example, contaminated water or food) and multiplies in the intestine. Initial symptoms are fever, fatigue, headache, vomiting, stiffness of the neck and pain in the limbs. One in 200 infections leads to irreversible paralysis (usually in the legs). Among those paralysed, 5% to 10% die when their breathing muscles become immobilized.

People most at risk: Polio mainly affects children under five years of age.

WHO Response

Launch of the Global Polio Eradication Initiative

In 1988, the Forty-first World Health Assembly adopted a resolution for the worldwide eradication of polio. It marked the launch of the Global Polio Eradication Initiative (GPEI), spearheaded by national governments, WHO, Rotary International, the US Centers for Disease Control and Prevention (CDC), UNICEF, and supported by key partners including the Bill and Melinda Gates Foundation. This followed the certification of the eradication of smallpox in 1980, progress during the 1980s towards elimination of the poliovirus in the Americas, and Rotary International's commitment to raise funds to protect all children from the disease.

Progress

Overall, since the GPEI was launched, the number of cases has fallen by over 99%. Today, only 2 countries in the world remain polio-endemic: Pakistan and Afghanistan.

In 1994, the WHO Region of the Americas was certified polio-free, followed by the WHO Western Pacific Region in 2000 and the WHO European Region in June 2002. On 27 March 2014, the WHO South-East Asia Region was certified polio-free, meaning that transmission of wild poliovirus has been interrupted in this bloc of 11 countries stretching from Indonesia to India. This achievement marks a significant leap forward in global eradication, with 80% of the world's population now living in certified polio-free regions.

Of the three types of wild poliovirus (type 1, type 2 and type 3), type 2 wild poliovirus transmission has been successfully stopped since 1999.

More than 15 million people are able to walk today, who would otherwise have been paralysed. An estimated 1.5 million childhood deaths have been prevented, through the systematic administration of vitamin A during polio immunization activities.

Opportunity and risks: an emergency approach

The strategies for polio eradication work when they are fully implemented. This is clearly demonstrated by India's success in stopping polio in January 2011, in arguably the most technically-challenging place, and polio-free certification of the entire South-East Asia Region of WHO occurred in March 2014.

Failure to implement strategic approaches, however, leads to ongoing transmission of the virus. Endemic transmission is continuing in Pakistan and Afghanistan. Failure to stop polio in these last remaining areas could result in as many as 200 000 new cases every year, within 10 years, all over the world.

Recognizing both the epidemiological opportunity and the significant risks of potential failure, the *"Polio Eradication and Endgame Strategic Plan 2013-2018"* has been developed, in consultation with polio-affected countries, stakeholders, donors, partners and national and international advisory bodies. The new Plan was presented at a Global Vaccine Summit in Abu Dhabi, United Arab Emirates, at the end of April 2013. It is the first plan to eradicate all types of polio disease simultaneously – both due to wild poliovirus and due to vaccine-derived polioviruses.

Future benefits of polio eradication

Once polio is eradicated, the world can celebrate the delivery of a major global public good that will benefit all people equally, no matter where they live. Economic modelling has found that the eradication of polio would save at least US$ 40–50 billion over the next 20 years, mostly in low-income countries. Most importantly, success will mean that no child will ever again suffer the terrible effects of lifelong polio-paralysis.

2. AGEING AND HEALTH

Overview

People worldwide are living longer. Today, for the first time in history, most people can expect to live into their sixties and beyond. By 2050, the world's population aged 60 years and older is expected to total 2 billion, up from 900 million in 2015. Today, 125

million people are aged 80 years or older. By 2050, there will be almost this many (120 million) living in China alone, and 434 million people in this age group worldwide. By 2050, 80% of all older people will live in low- and middle-income countries.

KEY FACTS

- Between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22%.
- By 2020, the number of people aged 60 years and older will outnumber children younger than 5 years.
- In 2050, 80% of older people will be living in low- and middle-income countries.
- The pace of population ageing is much faster than in the past.
- All countries face major challenges to ensure that their health and social systems are ready to make the most of this demographic shift.

The pace of population ageing around the world is also increasing dramatically. France had almost 150 years to adapt to a change from 10% to 20% in the proportion of the population that was older than 60 years .However, places such as Brazil, China and India will have slightly more than 20 years to make the same adaptation.

While this shift in distribution of a country's population towards older ages – known as population ageing - started in high-income countries (for example in Japan 30% of the population are already over 60 years old), it is now low- and middle-income countries that are experiencing the greatest change. By the middle of the century many countries for *e.g.* Chile, China, the Islamic Republic of Iran and the Russian Federation will have a similar proportion of older people to Japan.

A longer life brings with it opportunities, not only for older people and their families, but also for societies as a whole. Additional years provide the chance to pursue new activities such as further education, a new career or pursuing a long neglected passion. Older people also contribute in many ways to their families and communities. Yet the extent of these opportunities and contributions depends heavily on one factor: health. There is, however, little evidence to suggest that older people today are experiencing their later years in better health than their parents. While rates of severe disability have declined in high-income countries over the past 30 years, there has been no significant change in mild to moderate disability over the same period.

If people can experience these extra years of life in good health and if they live in a supportive environment, their ability to do the things they value will be little different from that of a younger person. If these added years are dominated by declines in physical and mental capacity, the implications for older people and for society are more negative.

Ageing explained

At the biological level, ageing results from the impact of the accumulation of a wide variety of molecular and cellular damage over time. This leads to a gradual decrease in physical and mental capacity, a growing risk of disease, and ultimately, death. But these changes are neither linear nor consistent, and they are only loosely associated with a person's age in years. While some 70 year-olds enjoy extremely good health and functioning, other 70 year-olds are frail and require significant help from others.

Beyond biological changes, ageing is also associated with other life transitions such as retirement, relocation to more appropriate housing, and the death of friends and partners. In developing a public-health response to ageing, it is important not just to consider approaches that ameliorate the losses associated with older age, but also those that may reinforce recovery, adaptation and psychosocial growth.

Common health conditions associated with ageing

Common conditions in older age include hearing loss, cataracts and refractive errors, back and neck pain and osteoarthritis, chronic obstructive pulmonary disease, diabetes, depression, and dementia. Furthermore, as people age, they are more likely to experience several conditions at the same time.

Older age is also characterized by the emergence of several complex health states that tend to occur only later in life and that do not fall into discrete disease categories. These are commonly called geriatric syndromes. They are often the consequence of multiple underlying factors and include frailty, urinary incontinence, falls, delirium and pressure ulcers.

Geriatric syndromes appear to be better predictors of death than the presence or number of specific diseases. Yet outside of countries that have developed geriatric medicine as a specialty, they are often overlooked in traditionally structured health services and in epidemiological research.

Factors influencing healthy ageing

Although some of the variations in older people's health are genetic, much is due to people's physical and social environments – including their homes, neighbourhoods, and communities, as well as their personal characteristics – such as their sex, ethnicity, or socioeconomic status.

These factors start to influence the ageing process at an early stage. The environments that people live in as children – or even as developing foetuses – combined with their personal characteristics, have long-term effects on how they age.

Environments also have an important influence on the development and maintenance of healthy behaviours. Maintaining healthy behaviours throughout life, particularly eating a balanced diet, engaging in regular physical activity, and refraining from tobacco use all contribute to reducing the risk of non-communicable diseases and improving physical and mental capacity.

Behaviours also remain important in older age. Strength training to maintain muscle mass and good nutrition can both help to preserve cognitive function, delay care dependency, and reverse frailty.

Supportive environments enable people to do what is important to them, despite losses in capacity. The availability of safe and accessible public buildings and transport, and environments that are easy to walk around are examples of supportive environments.

Challenges in responding to population ageing

Diversity in older age: There is no 'typical' older person. Some 80 year-olds have physical and mental capacities similar to many 20 year-olds. Other people experience significant declines in physical and mental capacities at much younger ages. A comprehensive public health response must address this wide range of older people's experiences and needs.

Health inequities: The diversity seen in older age is not random. A large part arises from people's physical and social environments and the impact of these environments on their opportunities and health behaviour. The relationship we have with our environments is skewed by personal characteristics such as the family we were born into, our sex and our ethnicity, leading to inequalities in health. A significant proportion of the diversity in older age is due to the cumulative impact of these health inequities across the life course. Public health policy must be crafted to reduce, rather than reinforce, these inequities.

Outdated and ageist stereotypes: Older people are often assumed to be frail or dependent, and a burden to society. Public health, and society as a whole, need to address these and other ageist attitudes, which can lead to discrimination, affect the way policies are developed and the opportunities older people have to experience Healthy Aging.

A rapidly changing world

Globalization, technological developments (*e.g.* in transport and communication), urbanization, migration and changing gender norms are influencing the lives of older people in direct and indirect ways. For example, although the number of surviving generations in a family has increased, today these generations are more likely than in the past to live separately. A public health response must take stock of these current and projected trends, and frame policies accordingly.

WHO's response

In accordance with a recent World Health Resolution (67/13), a comprehensive Global Strategy and Action Plan on Ageing and Health is being developed by WHO in consultation with Member States and other partners. The Strategy and Action Plan draws on the evidence of the World report on ageing and health and builds on existing activities to address 5 priority areas for action, as follows:-

Commitment to Healthy Ageing: Requires awareness of the value of Healthy Ageing and sustained commitment and action to formulate evidence-based policies that strengthen the abilities of older persons.

Aligning health systems with the needs of older populations: Health systems need to be better organized around older people's needs and preferences, designed to enhance older peoples intrinsic capacity, and integrated across settings and care providers.

Developing systems for providing long-term care: Systems of long-term care are needed in all countries to meet the needs of older people. This requires developing, sometimes from nothing, governance systems, infrastructure and workforce capacity.

Creating age-friendly environments: This will require actions to combat ageism, enable autonomy and support Healthy Ageing in all policies and at all levels of government.

Improving measurement, monitoring and understanding: Focused research, new metrics and analytical methods are needed for a wide range of ageing issues.

3. ROAD TRAFFIC INJURIES

Overview

Every year the lives of approximately 1.25 million people are cut short as a result of a road traffic crash. Between 20 and 50 million more people suffer non-fatal injuries, with many incurring a disability as a result of their injury.

Road traffic injuries cause considerable economic losses to victims, their families, and to nations as a whole. These losses arise from the cost of treatment (including rehabilitation and incident investigation) as well as reduced/lost productivity (e.g. in wages) for those killed or disabled by their injuries, and for family members who need to take time off work (or school) to care for the injured.

There are few global estimates of the costs of injury, but research carried out in 2010 suggests that road traffic crashes cost countries approximately 3% of their gross national product. This figure rises to 5% in some low- and middle-income countries.

Road traffic injuries have been neglected from the global health agenda for many years, despite being predictable and largely preventable. Evidence from many countries shows that dramatic successes in preventing road traffic crashes can be achieved through concerted efforts that involve, but are not limited to, the health sector.

KEY FACTS

- About 1.25 million people die each year as a result of road traffic crashes.
- Road traffic injuries are the leading cause of death among young people, aged 15–29 years.
- 90% of the world's fatalities on the roads occur in low- and middle-income countries, even though these countries have approximately half of the world's vehicles.
- Half of those dying on the world's roads are "vulnerable road users": pedestrians, cyclists and motorcyclists.
- Without action, road traffic crashes are predicted to rise to become the 7th leading cause of death by 2030.
- The newly adopted 2030 Agenda for Sustainable Development's has set an ambitious road safety target of halving the global number of deaths and injuries from road traffic crashes by 2020.

Who is at risk?

Socioeconomic status: More than 90% of deaths that result from road traffic injuries occur in low- and middle-income countries. Road traffic injury death rates are highest in the low- and middle-income countries of the African region. Even within high-income countries, people from lower socioeconomic backgrounds are more likely to be involved in a road traffic crashes.

Age: People aged between 15 and 44 years account for 48% of global road traffic deaths.

Sex: From a young age, males are more likely to be involved in road traffic crashes than females. About three-quarters (73%) of all road traffic deaths occur among men. Among young drivers, young males under the age of 25 years are almost 3 times as likely to be killed in a car crash as young females.

Risk factors and what can be done to address them

Road traffic injuries can be prevented. Governments need to take action to address road safety in a holistic manner, that requires involvement from multiple sectors (transport, police, health, education) and that addresses the safety of roads, vehicles, and road users themselves.

Effective interventions include designing safer infrastructure and incorporating road safety features into land-use and transport planning; improving the safety features of vehicles; and improving post-crash care for victims of road crashes. Interventions that target road user behaviour are equally important, such as setting and enforcing laws relating to key risk factors, and raising public awareness.

Key risk factors

Speed: An increase in average speed is directly related both to the likelihood of a crash occurring and to the severity of the consequences of the crash.

- An adult pedestrian's risk of dying is less than 20% if struck by a car at 50 km/h and almost 60% if hit at 80 km/h.
- 30 km/h speed zones can reduce the risk of a crash and are recommended in areas where vulnerable road users are common like residential and schools areas.
- Apart from reducing road traffic injuries, lower average traffic speeds can have other positive effects

on health outcomes (*e.g.* by reducing respiratory problems associated with car emissions).

Drink–driving: Drinking and driving increases both the risk of a crash and the likelihood that death or serious injury will result.

- The risk of being involved in a crash increases significantly above a blood alcohol concentration (BAC) of 0.04 g/dl.
- Laws that establish BACs of 0.05g/dl or below are effective at reducing the number of alcohol-related crashes.
- Enforcing sobriety checkpoints and random breath testing can lead to reductions in alcohol-related crashes of about 20% and have shown to be very cost-effective.
- Young and novice drivers are subject to an increased risk of road traffic crashes, when under the influence of alcohol, compared to older and more experienced drivers.
- Laws that establish lower BACs (≤0.02 g/dl) for young and novice drivers can lead to reductions in the number of crashes involving young people by up to 24%.

Motorcycle helmets

- Wearing a motorcycle helmet correctly can reduce the risk of death by almost 40% and the risk of severe injury by over 70%.
- When motorcycle helmet laws are enforced effectively, helmet wearing rates can increase to over 90%.
- Requiring helmets to meet recognized safety standards ensures that helmets can effectively reduce the impact of a collision to the head in the event of a crash.
- Seat-belts and child restraints
- Wearing a seat-belt reduces the risk of a fatality among front-seat passengers by 40–50% and of rear-seat passengers by between 25–75%.
- Mandatory seat-belt laws and their enforcement have been shown to be very effective at increasing seat-belt wearing rates.
- If correctly installed and used, child restraints reduce deaths among infants by approximately 70% and deaths among small children by between 54% and 80%.

Distracted driving: There are many types of distractions that can lead to impaired driving, but recently there has been a marked increase around the world in the use of mobile phones by drivers that is becoming a growing concern for road safety. The distraction caused by mobile phones can impair driving performance.Drivers using mobile phones may have: slower reaction times (notably braking reaction time, but also reaction to traffic signals), impaired ability to keep in the correct lane, and shorter following distances.

- Text messaging also results in considerably reduced driving performance, with young drivers at particular risk of the effects of distraction resulting from this use.
- Drivers using a mobile phone are approximately 4 times more likely to be involved in a crash than when a driver does not use a phone. Hands-free phones are not much safer than hand-held phone sets.
- While there is little concrete evidenceon how to reduce mobile phone use while driving, governments need to be proactive. Actions that can be taken include: adopting legislative measures, launching public awareness campaigns, and regularly collecting data on distracted driving to better understand the nature of this problem.

Providing technical support to countries

WHO works across the spectrum in countries, from primary prevention work to rehabilitation of those who have been involved in road traffic crashes. As such, WHO works in a multisectoral manner, in partnership with national stakeholders from a variety of sectors such as health, police, transport, education and other parties involved in road traffic injury prevention, including nongovernmental organizations and academics.

4. ANTIMICROBIAL RESISTANCE

What is antimicrobial resistance?

Antimicrobial resistance is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.

Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, such as antibacterial drugs (*e.g.* antibiotics), antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.

KEY FACTS

- Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.
- It is an increasingly serious threat to global public health that requires action across all government sectors and society.
- Antimicrobial resistance is present in all parts of the world. New resistance mechanisms emerge and spread globally.
- In 2012, WHO reported a gradual increase in resistance to HIV drugs, albeit not reaching critical levels. Since then, further increases in resistance to first-line treatment drugs were reported, which might require using more expensive drugs in the near future.
- In 2013, there were about 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB). Extensively drug-resistant tuberculosis (XDR-TB) has been identified in 100 countries. MDR-TB requires treatment courses that are much longer and less effective than those for non-resistant TB.
- In parts of the Greater Mekong subregion, resistance to the best available treatment for falciparum malaria, artemisinin-based combination therapies (ACTs), has been detected. Spread or emergence of multidrug resistance, including resistance to ACTs, in other regions could jeopardize important recent gains in control of the disease.
- There are high proportions of antibiotic resistance in bacteria that cause common infections (*e.g.* urinary tract infections, pneumonia, bloodstream infections) in all regions of the world. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant Gram-negative bacteria.
- Treatment failures due to resistance to treatments of last resort for gonorrhoea (third-generation cephalosporins) have been reported from 10 countries. Gonorrhoea may soon become untreatable as no vaccines or new drugs are in development.
- Patients with infections caused by drug-resistant bacteria are generally at increased risk of worse clinical outcomes and death, and consume more health-care resources than patients infected with the same bacteria that are not resistant.

The evolution of resistant strains is a natural phenomenon that occurs when microorganisms replicate themselves erroneously or when resistant traits are exchanged between them. The use and misuse of antimicrobial drugs accelerates the emergence of drug-resistant strains. Poor infection control practices, inadequate sanitary conditions and inappropriate food-handling encourage the further spread of antimicrobial resistance.

What is the difference between antibiotic and antimicrobial resistance?

Antibiotic resistance refers specifically to the resistance to antibiotics that occurs in common bacteria that cause infections. Antimicrobial resistance is a broader term, encompassing resistance to drugs to treat infections caused by other microbes as well, such as parasites (*e.g.* **malaria), viruses (***e.g.* **HIV) and fungi (***e.g. Candida***).**

Why is antimicrobial resistance a global concern?

New resistance mechanisms emerge and spread globally threatening our ability to treat common infectious diseases, resulting in death and disability of individuals who until recently could continue a normal course of life.

Without effective anti-infective treatment, many standard medical treatments will fail or turn into very high risk procedures.

Antimicrobial resistance kills

Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death.

As an example, the death rate for patients with serious infections caused by common bacteria treated in hospitals can be about twice that of patients with infections caused by the same non-resistant bacteria. For example, people with MRSA (methicillin-resistant *Staphylococcus aureus***,** another common source of severe infections in the community and in hospitals) are estimated to be 64% more likely to die than people with a non-resistant form of the infection.

Antimicrobial resistance hampers the control of infectious diseases

Antimicrobial resistance reduces the effectiveness of treatment; thus patients remain infectious for a longer time, increasing the risk of spreading resistant

microorganisms to others. For example, the emergence of *Plasmodium falciparum* multidrug resistance, including resistance to ACTs in the Greater Mekong subregion is an urgent public health concern that is threatening global efforts to reduce the burden of malaria.

Although MDR-TB is a growing concern, it is still largely under-reported, compromising control efforts.

Antimicrobial resistance increases the costs of health care

When infections become resistant to first-line drugs, more expensive therapies must be used. A longer duration of illness and treatment, often in hospitals, increases health care costs as well as the economic burden on families and societies.

Antimicrobial resistance jeopardizes health care gains to society

The achievements of modern medicine are put at risk by antimicrobial resistance. Without effective antimicrobials for prevention and treatment of infections, the success of organ transplantation, cancer chemotherapy and major surgery would be compromised.

Present situation

Resistance in bacteria: WHO's 2014 report on global surveillance of antimicrobial resistance revealed that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill.

- Treatment failure to the drug of last resort for gonorrhoea – third-generation cephalosporins – has been confirmed in several countries. Untreatable gonococcal infections result in increased rates of illness and complications, such as infertility, adverse pregnancy outcomes and neonatal blindness, and has the potential to reverse the gains made in the control of this sexually transmitted infection.
- Resistance to one of the most widely used antibacterial drugs for the oral treatment of urinary tract infections caused by *E. coli* – fluoroquinolones – is very widespread.
- Resistance to first-line drugs to treat infections caused by *Staphlylococcus aureus* – a common cause of severe infections acquired both in health-care facilities and in the community – is also widespread.
- Resistance to the treatment of last resort for life-threatening infections caused by common intestinal bacteria – carbapenem antibiotics – has spread to all regions of the world. Key tools to tackle antibiotic resistance – such as basic systems to track and monitor the problem – reveal considerable gaps. In many countries, they do not even seem to exist.

Resistance in tuberculosis

In 2013, there were an estimated 480 000 new cases of MDR-TB in the world. Globally, 3.5% of new TB cases and 20.5% of previously treated TB cases are estimated to have MDR-TB, with substantial differences in the frequency of MDR-TB among countries. Extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug) has been identified in 100 countries, in all regions of the world.

Resistance in malaria

The emergence of *P. falciparum* multidrug resistance, including resistance to ACTs, in the Greater Mekong subregion is an urgent public health concern that is threatening the ongoing global effort to reduce the burden of malaria. Routine monitoring of therapeutic efficacy is essential to guide and adjust treatment policies. It can also help to detect early changes in *P. falciparum* sensitivity to antimalarial drugs.

Resistance in HIV

HIV drug resistance emerges when HIV replicates in the body of a person infected with the virus who is taking antiretroviral drugs. Even when antiretroviral therapy (ART) programmes are very well-managed, some degree of HIV drug resistance will emerge.

Available data suggest that continued expansion of access to ART is associated with a rise in HIV drug resistance. In 2013, 12.9 million people living with HIV were receiving antiretroviral therapy globally, of which 11.7 million were in low- and middle-income countries.

HIV drug resistance may rise to such a level that the first-line and second-line ART regimens currently used to treat HIV become ineffective, jeopardizing people's lives and threatening national and global investments in ART programmes.

As of 2010, levels of HIV drug resistance among adults who had not begun treatment in countries

scaling up ART were found to be about 5% globally. However, since 2010, there are reports suggesting that pre-treatment resistance is increasing, peaking at 22% in some areas.

Continuous surveillance of HIV drug resistance is of paramount importance to inform global and national decisions on the selection of first and second-line ART and to maximize overall population level treatment effectiveness.

Resistance in influenza

Over the past 10 years, antiviral drugs have become important tools for treatment of epidemic and pandemic influenza. Several countries have developed national guidance on their use and have stockpiled the drugs for pandemic preparedness. The constantly evolving nature of influenza means that resistance to antiviral drugs is continuously emerging.

By 2012, virtually all influenza A viruses circulating in humans were resistant to drugs frequently used for the prevention of influenza (amantadine and rimantadine). However, the frequency of resistance to the neuraminidase inhibitor oseltamivir remains low (1-2%). Antiviral susceptibility is constantly monitored through the WHO Global Surveillance and Response System.

What accelerates the emergence and spread of antimicrobial resistance?

The development of antimicrobial resistance is a natural phenomenon. However, certain human actions accelerate its emergence and spread. The inappropriate use of antimicrobial drugs, including in animal husbandry, favours the emergence and selection of resistant strains, and poor infection prevention and control practices contribute to further emergence and spread of antimicrobial resistance.

Need for concerted actions

Antimicrobial resistance is a complex problem driven by many interconnected factors. As such, single, isolated interventions have little impact. Coordinated action is required to minimize emergence and spread of antimicrobial resistance.

People can help tackle resistance by:

- hand washing, and avoiding close contact with sick people to prevent transmission of bacterial infections and viral infections such as influenza or rotavirus, and using condoms to prevent the transmission of sexually-transmitted infections;
- getting vaccinated, and keeping vaccinations up to date;
- using antimicrobial drugs only when they are prescribed by a certified health professional;
- completing the full treatment course (which in the case of antiviral drugs may require life-long treatment), even if they feel better;
- never sharing antimicrobial drugs with others or using leftover prescriptions.

Health workers and pharmacists can help tackle resistance by:

- enhancing infection prevention and control in hospitals and clinics;
- only prescribing and dispensing antibiotics when they are truly needed;
- prescribing and dispensing the right antimicrobial drugs to treat the illness.

Policymakers can help tackle resistance by:

- improving monitoring around the extent and causes of resistance;
- strengthening infection control and prevention;
- regulating and promoting appropriate use of medicines;
- making information widely available on the impact of antimicrobial resistance and how the public and health professionals can play their part;
- rewarding innovation and development of new treatment options and other tools.

Policymakers, scientists and industry can help tackle resistance by:

- fostering innovation and research and development of new vaccines, diagnostics, infection treatment options and other tools.

WHO's response

WHO is guiding the response to antimicrobial resistance by:

- bringing all stakeholders together to agree on and work towards a coordinated response;
- strengthening national stewardship and plans to tackle antimicrobial resistance;
- generating policy guidance and providing technical support for Member States;
- actively encouraging innovation, research and development.

5. DENGUE AND SEVERE DENGUE

Overview

Dengue is a mosquito-borne viral disease that has rapidly spread in all regions of WHO in recent years. Dengue virus is transmitted by female mosquitoes mainly of the species *Aedes aegypti* and, to a lesser extent, *Ae. albopictus*. This mosquito also transmits chikungunya, yellow fever and Zika infection. Dengue is widespread throughout the tropics, with local variations in risk influenced by rainfall, temperature and unplanned rapid urbanization.

Severe dengue (also known as Dengue Hemorrhagic Fever) was first recognized in the 1950s during dengue epidemics in the Philippines and Thailand. Today, severe dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children in these regions.

KEY FACTS

- Dengue is a mosquito-borne viral infection.
- The infection causes flu-like illness, and occasionally develops into a potentially lethal complication called severe dengue.
- The global incidence of dengue has grown dramatically in recent decades. About half of the world's population is now at risk.
- Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas.
- Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.
- There is no specific treatment for dengue/ severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%.
- Dengue prevention and control depends on effective vector control measures.
- A dengue vaccine has been licensed by several National Regulatory Authorities for use in people 9 - 45 years of age living in endemic settings.

There are 4 distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4). Recovery from infection by one provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue.

Global burden of dengue

The incidence of dengue has grown dramatically around the world in recent decades. The actual numbers of dengue cases are under-reported and many cases are misclassified. One recent estimate indicates 390 million dengue infections per year (95% credible interval 284 –528 million), of which 96 million (67 - 136 million) manifest clinically (with any severity of disease)[1]. Another study, of the prevalence of dengue, estimates that 3.9 billion people, in 128 countries, are at risk of infection with dengue viruses[2].

Member States in 3 WHO regions regularly report the annual number of cases. In 2010, 2013 and 2015, nearly 2.4 million cases were reported annually. Although the full global burden of the disease is uncertain, the initiation of activities to record all dengue cases partly explains the sharp increase in the number of cases reported in recent years.

Other features of the disease include its epidemiological patterns, including hyper-endemicity of multiple dengue virus serotypes in many countries and the alarming impact on both human health and the global and national economies.

Before 1970, only nine countries had experienced severe dengue epidemics. The disease is now endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. The America, South-East Asia and Western Pacific regions are the most seriously affected.

Cases across the Americas, South-East Asia and Western Pacific exceeded 1.2 million in 2008 and over 3 million in 2013 (based on official data submitted by Member States). Recently the number of reported cases has continued to increase. In 2015, 2.35 million cases of dengue were reported in the Americas alone, of which 10,200 cases were diagnosed as severe dengue causing 1181 deaths.

Not only is the number of cases increasing as the disease spreads to new areas, but explosive outbreaks are occurring. The threat of a possible outbreak of dengue fever now exists in Europe as local transmission was reported for the first time in France and Croatia in 2010 and imported cases were detected in three other European countries. In 2012, an outbreak of dengue on the Madeira islands of Portugal resulted in over 2000 cases and imported cases were detected in mainland Portugal and 10 other countries in Europe. Among travelers returning from low- and middle-income countries, dengue is the second most diagnosed cause of fever after malaria.

In 2013, cases have occurred in Florida (United States of America) and Yunnan province of China. Dengue also continues to affect several South American countries, notably Costa Rica, Honduras and Mexico. In Asia, Singapore has reported an increase in cases after a lapse of several years and outbreaks have also been reported in Laos. In 2014, trends indicate increases in the number of cases in the People's Republic of China, the Cook Islands, Fiji, Malaysia and Vanuatu, with Dengue Type 3 (DEN 3) affecting the Pacific Island countries after a lapse of over 10 years. Dengue was also reported in Japan after a lapse of over 70 years.

The year 2015 was characterized by large dengue outbreaks worldwide, with the Philippines reporting more than 169,000 cases and Malaysia exceeding 111,000 suspected cases of dengue, representing a 59.5% and 16% increase in case numbers to the previous year, respectively.

Brazil alone reported over 1.5 million cases in 2015, approximately three times higher than in 2014. Also in 2015, Delhi, India, recorded its worst outbreak since 2006 with over 15,000 cases.

The Island of Hawaii, United States of America, was affected by an outbreak with 181 cases reported in 2015 and ongoing transmission in 2016. The Pacific island countries of Fiji, Tonga and French Polynesia have continued to record cases.

An estimated 500 000 people with severe dengue require hospitalization each year, a large proportion of whom are children. About 2.5% of those affected die.

WHO/TDR/Stammers: The *Aedes aegypti* mosquito is the primary vector of dengue. The virus is transmitted to humans through the bites of infected female mosquitoes. After virus incubation for 4 - 10 days, an infected mosquito is capable of transmitting the virus for the rest of its life.

Infected symptomatic or asymptomatic humans are the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes. Patients who are already infected with the dengue virus can transmit the infection (for 4 - 5 days; maximum 12) via *Aedes* mosquitoes after their first symptoms appear.

The *Aedes aegypti* mosquito lives in urban habitats and breeds mostly in man-made containers. Unlike other mosquitoes, *Ae. aegypti* is a day-time feeder; its peak biting periods are early in the morning and in the evening before dusk. Female *Ae. aegypti* bites multiple people during each feeding period.

Aedes albopictus, a secondary dengue vector in Asia, has spread to North America and more than 25 countries in the European Region, largely due to the international trade in used tyres (a breeding habitat) and other goods (*e.g.* lucky bamboo). *Ae. albopictus* is highly adaptive and, therefore, can survive in cooler temperate regions of Europe. Its spread is due to its tolerance to temperatures below freezing, hibernation, and ability to shelter in microhabitats.

Characteristics

Dengue fever is a severe, flu-like illness that affects infants, young children and adults, but seldom causes death.

Dengue should be suspected when a high fever (40 °C/104 °F) is accompanied by two of the following symptoms: severe headache, pain behind the eyes, muscle and joint pains, nausea, vomiting, swollen glands or rash. Symptoms usually last for 2 - 7 days, after an incubation period of 4 -10 days after the bite from an infected mosquito.

Severe dengue is a potentially deadly complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Warning signs occur 3 - 7 days after the first symptoms in conjunction with a decrease in temperature (below 38 °C/100 °F) and include: severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, fatigue, restlessness and blood in vomit. The next 24 - 48 hours of the critical stage can be lethal; proper medical care is needed to avoid complications and risk of death.

Treatment

There is no specific treatment for dengue fever.

For severe dengue, medical care by physicians and nurses experienced with the effects and progression of the disease can save lives – decreasing mortality rates from more than 20% to less than 1%. Maintenance of the patient's body fluid volume is critical to severe dengue care.

Immunization

In late 2015 and early 2016, the first dengue vaccine, Dengvaxia (CYD-TDV) by Sanofi Pasteur, was registered in several countries for use in individuals 9-45 years of age living in endemic areas. The Strategic Advisory Group of Experts (SAGE) on immunization reviewed CYD-TDV in April 2016 and recommended countries consider introduction of the vaccine in

geographic settings (national or subnational) with high endemicity. A WHO Vaccine Position Paper will be published outlining WHO recommendations in July 2016.

Other tetravalent live-attenuated vaccines are under development in phase II and phase III clinical trials, and 3 other vaccine candidates (based on subunit, DNA and purified inactivated virus platforms) are at earlier stages of clinical development. WHO provides technical advice and guidance to countries and private partners to support vaccine research and evaluation.

Prevention and control

WHO/TDR/Crump: At present, the main method to control or prevent the transmission of dengue virus is to combat vector mosquitoes through:

- preventing mosquitoes from accessing egg-laying habitats by environmental management and modification;
- disposing of solid waste properly and removing artificial man-made habitats;
- covering, emptying and cleaning of domestic water storage containers on a weekly basis;
- applying appropriate insecticides to water storage outdoor containers;
- using of personal household protection such as window screens, long-sleeved clothes, insecticide treated materials, coils and vaporizers;
- improving community participation and mobilization for sustained vector control;
- applying insecticides as space spraying during outbreaks as one of the emergency vector-control measures;
- active monitoring and surveillance of vectors should be carried out to determine effectiveness of control interventions.

1. Bhatt S, Gething PW, Brady OJ, *et.al.* The global distribution and burden of dengue. Nature 2013; 496:504-507.
2. Brady OJ, Gething PW, Bhatt S, *et al***.** Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis 2012; 6:e1760. doi:10.1371/journal.pntd.0001760.