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Are We Barking Up the Wrong Tree?

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##

"You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all the people all the time."

Abraham Lincoln

What worries me is the news item that when the doctors in Israel went on strike in March 2000, death rate fell significantly in Jerusalem city, while it did not change in the coastal city of Netanya, where doctors worked as usual [1]. Even when compared to the month of March in 1999 and 1998, the fall in death rate in 2000 was noteworthy. Similar trend was reported from Los Angeles County (USA) in the 1970s and, possibly, also in Canada and Bogota in Columbia a few years ago. Even in the field of drug trials, small studies seem to give striking benefit, but under further investigations they “do not deliver the degree of benefit initially touted by their clinical champions and marketers. All is not well in our thinking in this area”.

While the life expectancy seems to have gone up in the developed countries, mainly because of the change of mode of living and better standards of living, human life span has not gone up. Health expectancy (a word I coined to denote the number of years a new-born baby could expect to live without the help of doctors and medicines) seems to have come down in the industrialized countries. Hardly anyone in the West goes beyond the age of ten without having to be taking multivitamin and many other pills almost as a part of their diet! In fact, health expectancy is quite high in some of the developing countries like India, where people in villages live almost their full lives without any medical interventions; the life expectancy being 67 years.

There is hardly a “well man” in the developed West, what with routine screening making life miserable, to say the least, despite the fact that a recent editorial in the British Medical Journal avers that routine screening could seriously damage one’s health[3]. Modern quantum physics makes a mockery of future predictions in any dynamic system without the total initial knowledge of the organism. Doctors have been predicting the unpredictable. To predict man’s future, his doctor should have complete knowledge of his phenotype, genotype and his consciousness. That seems to be impossible in the present state of our knowledge[3].

Diseases originate in the human mind (consciousness), the seeds being negative thoughts like greed, jealousy, hatred, anger, and depression[4]. If sown in a genetically fertile soil (with the correct genetic pattern), the seeds could grow well into the final tree (disease) with all its ramifications, when fed by the help of a conducive atmosphere, including tobacco and alcohol, which work like the best manure for the crop. Management, therefore, should take into consideration all these together; not just the changes in the phenotype. The latter has not taken us too far!

Now with quantum physics trying to understand human consciousness, time has come for modern medicine to divorce itself from the time-honoured reductionist logic of linear relations in dynamic systems. It is a pity that after so many fantastic claims of advances in medical science we have been able to eradicate only one disease, small pox. Incidentally, that was not being done with any advanced technology! Edward Jenner, credited to be the father of vaccination, had to have his method authenticated and refined,
with the help of a long term (twenty year) prospective study of the Indian system of vaccination, practised there for centuries with nearly 90% success rate, by a Fellow of the Royal College of Physicians of London, Dr. T. Z. Holwell, in the year 1747. Holwell spent many years in India to study the system of vaccination with attenuated virus[9].

The directionless movement of mankind with the industrial revolution where value systems have been given a go by, resulting in even High School children shooting their peers for petty jealousies, we better move fast to keep them healthy on this planet. Let the wisdom of the human body play its part in the game of healthy living! Let not the medical fraternity think they are wiser than the body’s wisdom[10].

To compound our confusion, we have been targeting these midway changes (like raised BP, sugar, fats, etc.) as the cause of diseases and trying to reduce and / or correct them mostly with disastrous results, as noted above! Proper audits of our interventions have shown that many of the technologies, not to speak of drugs, have done more harm than good. Many midway technologies have never been audited at all! Many of the interventions in the intensive care units fall into this last category. The famous MRFIT study did show that while the risk factors could be modified by our interventions, the final RISK of precocious death can not be prevented[11].

Antioxidant vitamins did not do much good compared to eating extra fruits and vegetables in a large group of Canadian postmenopausal women. Whereas some studies did show benefit from eating fish, larger studies did not show any difference between those that eat fish daily compared to those who eat fish once in a blue moon. Long term prospective studies did not show any benefit from regular screening and correcting the biochemical abnormalities in asymptomatic individuals[12]. In conclusion, it is the body’s wisdom that keeps us going despite the medical industry’s efforts to make us their clients for their business!

“I was brought up to believe that the only thing worth doing was to add to the sum of accurate information in the world.” Margaret Mead

REFERENCES

Review Article

Ortner (Cardio-vocal) Syndrome: A Collective Review

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Kuwait Medical Journal 2014; 46 (1): 3 - 13

ABSTRACT

To understand the concept of Ortner’s (cardio-vocal) syndrome (OCVS), it is necessary to present the up-to-date clinical features and potential management strategies of cardiovascular hoarseness. The medical literature on OCVS published between 1980 and 2011 was comprehensively retrieved and analyzed. The patients who had cardiovascular hoarseness included a total of 256 patients. Hoarseness was the only symptom in 91 (35.27%) patients. The secondary symptoms of patients varied greatly, with dyspnea and dysphagia being the most common manifestations. OCVS is uncommon. Aortic aneurysms of various etiologies are the most common risk factors leading to cardiovascular hoarseness. When a patient presents with hoarseness, one should never overlook the cardiovascular causes, so that a misdiagnosis can be avoided and an immediate therapy is started.

KEYWORDS: aortic disease, congenital, heart defects, hoarseness, mitral valve stenosis

INTRODUCTION

Numerous conditions ranging from the common cold to systemic disorders involving the larynx can cause hoarseness[1-2]. The cause may be neoplastic (32%), surgical (30%), idiopathic (16%), traumatic (11%), central (8%) or infectious (3%) [3]. In recurrent laryngeal nerve paralysis, the left recurrent laryngeal nerve (LRLN) was more commonly involved than the right (70% Vs 30%) [4-5]. The diagnosis is usually based on the patient’s medical history, physical examination, and computed tomographic (CT) scan or magnetic resonance imaging (MRI) results [5-6].

Hoarseness due to LRLN palsy caused by cardiovascular disease is termed as OCVS as described by Ortner in 1897 [5-6]. Subsequently, this condition was reported to be associated with series of cardiovascular disorders including congenital heart defects, aortic disease, mitral valve insufficiency, and pulmonary hypertension. In the past decades, more and more patients with hoarseness of voice caused by left vocal cord palsy resulting from cardiovascular disorders have been reported. To understand the concept of this peculiar entity, it is necessary to present an up-to-date review of clinical features and potential management strategies of cardiovascular hoarseness.

MATERIALS AND METHODS

Retrieval policies

The medical literature on OCVS published between 1980 and 2011 was comprehensively retrieved in the MEDLINE database and the Google and Highwire Press search engines. The secondary references cited in the articles obtained from these sources were screened. Articles published in Mandarin in mainland China journals were excluded from this study. An article published in the European Journal of Medicine, 1992, was considered to be a repetitive publication in terms of majority of their case series to an alternative article published by the same first author, and hence to be removed. However, the articles written in Mandarin published in the medical journals in Taiwan were included. The search ended on December 21, 2011.

Statistics

Data were expressed in mean ± standard deviation and student ‘t’ test was used to evaluate intergroup differences. A p-value of < 0.05 was considered to be statistically significant.

RESULTS

By comprehensive literature collection, a total of 256 patients had cardiovascular hoarseness including
245 cases from 172 reports and 11 cases from the cited references of the report of Myojin et al.

Out of the patients whose gender was recorded, there were 101 male and 55 female patients with a male-to-female ratio of 1.84:1. Their mean age was 53.90 ± 22.76 years (range, from 6 days to 90 years) (n = 196). No age difference was found between male and female patients (55.59 ± 22.09 years, Vs 50.93 ± 23.76 years, p = 0.1686). Two hundred and eight patients had their age range recorded. There were 17 minors, children and infants (8.17%) ≤ 17 years old (age range, 6 days ~ 17 years; mean age, 5.21 ± 7.15 years; median age, 0.58 years) and the remaining 189 (91.83%) patients were ≥ 18 years old (age range, 18 ~ 90 years, mean age, 58.24 ± 18.11 years; median age, 62 years). The patients' age distribution is shown in Fig. 1.

All patients in this patient setting presented with hoarseness. The nature of hoarseness was not described in majority of the reports, while in a few, it was described as gradual or progressive. Hoarseness was the only symptom in 91 (35.27%) patients. Besides, the secondary symptoms of the patients varied greatly, with dyspnea and dysphagia being the most common manifestations (Table 1). In addition, 61 patients had a past medical history (Table 2). The duration of hoarseness was 10.09 ± 19.66 (range, -2 ~ 120) months (n = 120) (minus means the onset of hoarseness developed after admission), with no difference between males and females (8.60 ± 17.57 months Vs 13.84 ± 23.83 months, p = 0.1846), or between the minors and adults (3.59 ± 3.61 months Vs 10.82 ± 20.47 months, p = 0.2691). No significant relationship was found between the patients' age and the duration of hoarseness (Y = 0.002X + 10.101, R² = 5×10⁻²) (Fig. 2).

Left vocal cord paralysis was verified by laryngoscopy in 140 (54.26%) patients and bilateral vocal cord paralysis in one (0.39%) patient, of which the resting positions of the vocal cord were recorded in 32 patients: the vocal cords were resting in the paramedian position in 27 (84.38%) patients and in the median position in 5 (15.63%) patients. Vocal cord position and movement under laryngoscopy in 141 patients with OCVS are shown in Table 3.

In the early days, angiogram, surgical exploration or autopsy was the diagnostic method for OCVS. Nowadays, non-invasive modalities including echocardiography, CT scan and MRI have mostly substituted the invasive catheterization as the diagnostic means. However, angiogram is still an adjunct on some occasions (Table 4).
Fourteen patients had their C-reactive protein (CRP) measured. It was reported that one patient had a normal CRP value without giving any quantitative result. The remaining 13 patients had a CRP of 10.20 ± 11.02 (range, 0.1 - 30.63, median 5) mg/dl.

Out of the young patients ≤ 17 years of age, in infants, congenital heart disease prevailed as an underlying cause of hoarseness including atrial or ventricular septal defect (ASD and VSD), patent ductus arteriosus (PDA), total anomalous pulmonary venous connection, double outlet right ventricle, left main coronary artery arising from the pulmonary artery, or idiopathic pulmonary artery hypertension.

In older children, rheumatic mitral stenosis was the most common. Inclusive of a 16-year-old patient who had a traffic accident which caused aortic arch rupture, aortic disorders were the most common underlying causes of OCVS in 142 (55.47%) patients. Aortic aneurysms of various etiologies showed overwhelming predilections leading to left vocal cord palsy and hoarseness in 132 (51.56%) patients. Moreover, left atrial lesions presented in 20 (7.81%), and congenital heart defects presented in 14 (5.47%) patients, respectively. Ductal aneurysms, either patent or non-patient, accounted for up to 22 (8.59%) patients (Table 5).

### Table 2: Past history of 61 patients with Ortner (cardiovascular) syndrome

<table>
<thead>
<tr>
<th>Past history</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia, ankylosing spondylitis, hepatitis B, cocaine abuse</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Atrial fibrillation, stroke</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Blunt chest trauma (traffic accident, falling from height)</td>
<td>13 (21.3)</td>
</tr>
<tr>
<td>Chronic atrial fibrillation</td>
<td>2 (3.28)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2 (3.28)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, s/p coronary artery bypass grafting</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (8.20)</td>
</tr>
<tr>
<td>Coronary artery disease/myocardial infarction, hypertension</td>
<td>2 (3.28)</td>
</tr>
<tr>
<td>Diabetes, pneumonia, upper lung abscess</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Human immunodeficiency virus and hepatitis C virus infections, hemophilia</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (9.84)</td>
</tr>
<tr>
<td>Hypertension, chronic obstructive pulmonary disease, chronic renal failure</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Hypertension, coronary artery disease, s/p percutaneous transluminal coronary angioplasty</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Hypertension, gouty arthritis</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Hypertension, hypertensive renal disease</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Lung cancer invasion</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Myocardial infarction, s/p percutaneous coronary interventions</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Osteomyelitis of the right tibia</td>
<td>1 (1.64)</td>
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<tr>
<td>Raynaud’s phenomenon, meningoraña, systemic lupus erythematosus</td>
<td>1 (1.64)</td>
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<tr>
<td>Retrotracheal aorta with aberrant left carotid artery</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Rheumatoid arthritis, peripheral vasculitis</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Adrenalectomy, unrepaird aortic abdominal aneurysm (s/p)</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Coronary artery bypass grafting (s/p)</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Heart transplantation (s/p)</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Hemicolecotomy for colon cancer, fistula in the esophagol wall (s/p)</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Mitral valve replacement (s/p)</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Patent ductus arteriosus ligation (s/p)</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Repair of coaetation of the aorta 34 years earlier (s/p)</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Schistosomiasis mansoni</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Schistosomiasis, urinary and intestinal</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Superior vena cava syndrome</td>
<td>1 (1.64)</td>
</tr>
<tr>
<td>Tuberculosis, pulmonary</td>
<td>3 (4.92)</td>
</tr>
<tr>
<td>Tuberculosis, military</td>
<td>1 (1.64)</td>
</tr>
</tbody>
</table>

### Table 3: Vocal cord situation and movement under laryngoscopy of 141 patients with Ortner (cardiovascular) syndrome

<table>
<thead>
<tr>
<th>Situation and movement</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Situation</td>
<td>127 (100)</td>
</tr>
<tr>
<td>Completely paralyzed</td>
<td>7 (5.51)</td>
</tr>
<tr>
<td>Paralyzed</td>
<td>80 (56.74)</td>
</tr>
<tr>
<td>Palsy</td>
<td>33 (25.98)</td>
</tr>
<tr>
<td>Subtle palsy</td>
<td>1 (0.79)</td>
</tr>
<tr>
<td>Paraesis</td>
<td>2 (1.57)</td>
</tr>
<tr>
<td>Partially paralyzed</td>
<td>2 (1.57)</td>
</tr>
<tr>
<td>Closure</td>
<td>1 (0.79)</td>
</tr>
<tr>
<td>Deviation</td>
<td>1 (0.79)</td>
</tr>
<tr>
<td>Movement</td>
<td>14 (10.0)</td>
</tr>
<tr>
<td>Immobile/fixation</td>
<td>9 (6.42)</td>
</tr>
<tr>
<td>Slightly movable</td>
<td>2 (1.42)</td>
</tr>
<tr>
<td>Reduced mobility</td>
<td>1 (0.71)</td>
</tr>
<tr>
<td>Negligible movement</td>
<td>1 (0.71)</td>
</tr>
<tr>
<td>Standstill</td>
<td>1 (0.71)</td>
</tr>
</tbody>
</table>

### Table 4: Diagnostic methods in 174 patients

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>39 (22.41)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>31 (17.82)</td>
</tr>
<tr>
<td>Angiogram</td>
<td>31 (17.82)</td>
</tr>
<tr>
<td>CT + angiogram</td>
<td>27 (15.52)</td>
</tr>
<tr>
<td>CT + echocardiography</td>
<td>9 (5.17)</td>
</tr>
<tr>
<td>CT + MRI</td>
<td>8 (4.60)</td>
</tr>
<tr>
<td>Echocardiography + angiogram</td>
<td>5 (2.87)</td>
</tr>
<tr>
<td>MRI</td>
<td>3 (1.72)</td>
</tr>
<tr>
<td>CT + echocardiography + angiogram</td>
<td>3 (1.72)</td>
</tr>
<tr>
<td>CT + MRI + angiogram</td>
<td>2 (1.15)</td>
</tr>
<tr>
<td>CT + MRA</td>
<td>2 (1.15)</td>
</tr>
<tr>
<td>Surgical exploration</td>
<td>4 (2.30)</td>
</tr>
<tr>
<td>Autopsy</td>
<td>2 (1.15)</td>
</tr>
<tr>
<td>Barium swallow examination</td>
<td>1 (0.57)</td>
</tr>
<tr>
<td>CT + CTA</td>
<td>1 (0.57)</td>
</tr>
<tr>
<td>CT + CT-guided needle biopsy</td>
<td>1 (0.57)</td>
</tr>
<tr>
<td>CT + MRI + MRA</td>
<td>1 (0.57)</td>
</tr>
<tr>
<td>CTA</td>
<td>1 (0.57)</td>
</tr>
<tr>
<td>Echocardiography + MRI</td>
<td>1 (0.57)</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>1 (0.57)</td>
</tr>
<tr>
<td>Upper gastrointestinal endoscopy</td>
<td>1 (0.57)</td>
</tr>
</tbody>
</table>

CT = computed tomography, CTA = computed tomographic angiogram, MRA = magnetic resonance angiogram, MRI = magnetic resonance imaging
Table 5: Primary disorders responsible for cardiovascular hoarseness

<table>
<thead>
<tr>
<th>Primary disorders</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart defects</td>
<td>14 (5.47)</td>
</tr>
<tr>
<td>Patent ductus arteriosus + pulmonary artery hypertension</td>
<td>3</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>1</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular septal defect + patent ductus arteriosus</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>1</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>1</td>
</tr>
<tr>
<td>Ebstein’s anomaly</td>
<td>1</td>
</tr>
<tr>
<td>Mitral atresia</td>
<td>1</td>
</tr>
<tr>
<td>Double outlet right ventricle with mitral atresia</td>
<td>1</td>
</tr>
<tr>
<td>Ensenmenger’s syndrome, large ventricular septal defect</td>
<td>1</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous connection</td>
<td>1</td>
</tr>
<tr>
<td>Left atrial disorders</td>
<td>20 (7.81)</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>9</td>
</tr>
<tr>
<td>Mitral regurgitation + mitral stenosis</td>
<td>2</td>
</tr>
<tr>
<td>Mitral regurgitation + aortic regurgitation</td>
<td>1</td>
</tr>
<tr>
<td>Mitral stenosis with pulmonary hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Mitral periprostheses insufficiency with severe pulmonary hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>3</td>
</tr>
<tr>
<td>Left atrial myxoma</td>
<td>1</td>
</tr>
<tr>
<td>Chorda tendinae rupture</td>
<td>1</td>
</tr>
<tr>
<td>Aortic diseases</td>
<td>142 (55.47)</td>
</tr>
<tr>
<td>Aortic rupture (traumatic)</td>
<td>1</td>
</tr>
<tr>
<td>Penetrating aortic ulcer</td>
<td>2</td>
</tr>
<tr>
<td>Infectious aortitis</td>
<td>1</td>
</tr>
<tr>
<td>Giant cell arthritis of the aorta</td>
<td>1</td>
</tr>
<tr>
<td>Aortic fistulae</td>
<td>5</td>
</tr>
<tr>
<td>Esophago-broncho-aortic fistula</td>
<td>1</td>
</tr>
<tr>
<td>Aortopulmonary and/or aortoesophageal fistula</td>
<td>1</td>
</tr>
<tr>
<td>Aortobronchial fistula</td>
<td>1</td>
</tr>
<tr>
<td>Acute aorto-pulmonary artery fistula</td>
<td>1</td>
</tr>
<tr>
<td>Aortotraceal fistula</td>
<td>1</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>132</td>
</tr>
<tr>
<td>Marfan: Root (1)</td>
<td>1</td>
</tr>
<tr>
<td>Atherosclerotic: Aorta (8), arch (11), proximal descending aorta (1)</td>
<td>20</td>
</tr>
<tr>
<td>Degenerative: Aorta (4), arch (5), descending aorta (1), arch + descending aorta (1)</td>
<td>11</td>
</tr>
<tr>
<td>Embryologic: Arch (1)</td>
<td>1</td>
</tr>
<tr>
<td>Tuberculosis: Arch (2)</td>
<td>2</td>
</tr>
<tr>
<td>Syphilitic</td>
<td>2</td>
</tr>
<tr>
<td>Myotic</td>
<td>10</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>3</td>
</tr>
<tr>
<td>Inflammatory: Arch + right subclavian artery + infrarenal abdominal aorta (1)</td>
<td>1</td>
</tr>
<tr>
<td>Not described: Aorta (16), arch (16) [one of them ruptured into the pulmonary artery], isthmus (2), descending aorta (11)</td>
<td>45</td>
</tr>
<tr>
<td>Traumatic: Aorta (8), arch (4), proximal descending aorta (6), arch + descending aorta (1)</td>
<td>19</td>
</tr>
<tr>
<td>Dissecting: Aorta (posttraumatic) (5), arch (6), descending aorta (5), ascending + arch + descending (1)</td>
<td>17</td>
</tr>
<tr>
<td>Supraaortic vessel disorders</td>
<td>16 (6.25)</td>
</tr>
<tr>
<td>Aberrant right subclavian artery aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Aneurysm of the common carotid artery (Takayasu’s arteritis)</td>
<td>1</td>
</tr>
<tr>
<td>Aneurysm of the innominate artery</td>
<td>1</td>
</tr>
<tr>
<td>Aneurysm of the right subclavian artery</td>
<td>2</td>
</tr>
<tr>
<td>Aneurysm of the right subclavian artery + ascending aorta dilation</td>
<td>1</td>
</tr>
<tr>
<td>Anomalous left carotid artery arising from a retrotracheal arch</td>
<td>1</td>
</tr>
<tr>
<td>Left subclavian artery pseudeaneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Pseudoaneurysm of the innominate artery (myotic)</td>
<td>1</td>
</tr>
<tr>
<td>Pseudoaneurysm of the right subclavian artery</td>
<td>1</td>
</tr>
<tr>
<td>Pseudoaneurysm of the left common carotid artery</td>
<td>1</td>
</tr>
<tr>
<td>Right subclavian artery aneurysm (tuberculosis)</td>
<td>1</td>
</tr>
<tr>
<td>Right subclavian artery aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Right subclavian artery pseudeaneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Ruptured innominate artery</td>
<td>1</td>
</tr>
<tr>
<td>Tortuosity of the three aortic branches</td>
<td>1</td>
</tr>
<tr>
<td>Other cardiovascular malformations</td>
<td>54 (21.09)</td>
</tr>
<tr>
<td>Aneurysm of diverticulm of the ductus arteriosus</td>
<td>7</td>
</tr>
<tr>
<td>Chronic cor pulmonale</td>
<td>2</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1</td>
</tr>
</tbody>
</table>

Continued...
Table 5 Continues ...  

<table>
<thead>
<tr>
<th>Primary disorders</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal aneurysm</td>
<td>22</td>
</tr>
<tr>
<td>Left ventricular aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary artery aneurysm</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary artery dilation</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary artery hypertension</td>
<td>8</td>
</tr>
<tr>
<td>Schistosomal pulmonary hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Pericardial cyst</td>
<td>1</td>
</tr>
<tr>
<td>Extracardiac lesions</td>
<td>10 (3.91)</td>
</tr>
<tr>
<td>Massive hepatic hemangiomatosis (extracardiac vascular abnormality leading to dilatation of the left atrium)</td>
<td>1</td>
</tr>
<tr>
<td>Cystic fibrosis of the lung</td>
<td>1</td>
</tr>
<tr>
<td>Tumor of the Botallo’s lymph node invading the aortic arch</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal fibromatosis</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal bronchial artery aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>High altitude</td>
<td>3</td>
</tr>
<tr>
<td>Adenocarcinoma of the thymus</td>
<td>1</td>
</tr>
</tbody>
</table>

Out of the total patients, 16 (6.25%) patients died. The management of the underlying primary disorders responsible for the hoarseness in 90 patients was surgical in 41 (45.56%), interventional in 12 (13.33%), and follow-up / conservative treatment in 37 (41.11%). Two (2.22%) patients refused surgery, and two (2.22%) patients refused interventional treatment. Out of three patients who received treatment for the hoarseness, two had thyroplasty and one patient received injection and the voice recovered. The remaining patients did not. Forty patients had a follow-up of two weeks ~ 6 years (mean, 8.51 ± 12.13 months; median 5.5 months). The outcomes of hoarseness were recorded in 58 patients: resolved in 26 (44.83%), improved in 17 (29.31%), persisted in 13 (22.41%), and exacerbated in two (3.45%) patients, respectively.

DISCUSSION

Anatomy

The LRLN courses between the aorta and pulmonary artery. Cadaveric studies illustrated that the distance between the aorta and pulmonary artery within the aortic window is only 4 mm. Therefore, the primary mechanism of injury to the LRLN involves compression of the nerve between the left pulmonary artery and aorta[177]. Ari et al[178] found that the LRLN was compressed between an enlarged left pulmonary artery and aorta near the ligamentum arteriosum in patients with mitral stenosis. However, it may have anatomical variance in certain individuals. Odegard et al[179] observed during video-assisted thoracoscopic surgery for PDA, LRLN had an unexpected location in 8 / 59 (13.56%) patients: in direct contact with the PDA on its superior surface in 5 / 59 (8.47%), on its lateral surface in 2 / 59 (3.39%) and beyond this region in 1 / 59 (1.69%) patients, respectively. In 29 / 59 (49.15%) patients, it was located inferiorly and medially to the ductus with close proximity to the position for placing a clip and thus vulnerable to injury.

Symptomatology

Hoarseness caused by cardiovascular pathology might be the only symptom for the patients to consult a clinician[134]. Alternative symptoms may include dyspnea, wheezing, or hemoptysis resulting from laryngeal nerve impingement, or chest pain caused by hemorrhage or compression of the intrathoracic structures[180]. The ductal aneurysm may compress the left main bronchus thereby explaining the wheeze[53]. Most fistulas are related to the thoracic aortic aneurysm, and massive hemoptysis has been reported in these patients[181]. Hoarseness can be the initial manifestation of a painless aortic pseudoaneurysm formed by an aortotraheal fistula[157]. When the patients with OCVS syndrome presents with hemoptysis, lethal aorto-pulmonary fistula should be highly suspected[157]. The movement and status of the vocal cord may have close correlation with the severity of the symptoms. Resting in a paramedian position for the LRLN may result in an absence of vocal fold opposition, weak phonation, stridor and feeding difficulties in infants due to poor swallowing coordination or aspiration through an incompetent larynx[182]. Vocal cord fixation may mean that the vocal cord becomes atrophic, hoarseness becomes exacerbated, or aspiration may be associated with vocal cord adduction; when the vocal cord becomes movable, symptoms such as hoarseness and aspiration could be alleviated[60].

Etiology

In OCVS, the LRLN was injured by compression or traction resulting from the cardiovascular anatomical changes[134]. Clinical observations revealed that the aortic aneurysms were located in the aortic arch, proximal part of descending aorta, or distal part of the arch. All of them had close proximity to the aortic arch / isthmus[60] and the LRLN was stretched over the aneurysm[34,143]. The shapes of the aortic aneurysms leading to OCVS varied, being saccular, fusiform, cystic
or dissecting. Stooob et al described that the shapes of the aneurysms did not correlate with the clinical outcomes. In addition, aortic aneurysm complicating aorto-bronchopulmonary and aorto-esophageal fistulae may also present with hoarseness.

Pseudoaneurysms are frequently post-traumatic, atherosclerotic, inflammatory (vasculitic) and infectious (mycotic) in origin. Pseudoaneurysm formation in Behcet’s disease was taken as obliteration in infectious (mycotic) in origin, and LRLN palsy was actually an ‘immediate hoarseness’ complication following cardiovascular operation, intervention or maneuver. On the contrary, a hoarse voice caused by leaf complications secondary to cardiovascular operations like aortic pseudoaneurysms should be termed as iatrogenic OCVS. Instead, the hoarse voice occurring following cardiovascular operation, intervention or maneuver should be defined as an “immediate hoarse complication”, “iatrogenic LRLN palsy” or “iatrogenic left vocal cord paralysis”. Therefore, the usually mentioned “iatrogenic left vocal cord paralysis” was a wrong concept and should be excluded from the domain of OCVS. The bias in this concept should be realized by all concerned.

CONCLUSIONS

OCVS is uncommon. Aortic aneurysms of various etiologies are the most common risk factors leading to cardiovascular hoarseness. The location of the aneurysms near the aortic arch correlated significantly with the development of cardio-vocal hoarseness. When the patient presents with hoarseness, one should never overlook the cardiovascular causes so that a misdiagnosis is avoided and an immediate therapy is started.

REFERENCES


79. Schneider B, Czerny C, Baumgartner H, Zehetgruber M, Bigenzahn W. Der Ductus arteriosus apertus


Central Nervous System Manifestation in Patients with SLE: A 12-Year Retrospective Chart Review at a Tertiary Center

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ABSTRACT

Background: Central nervous system manifestation of systemic lupus erythematosus (CNS-SLE) is a common complication, which is clinically associated with patient morbidity and mortality

Objective: To determine the CNS-SLE manifestations and to determine the predictors of death among the studied cohort

Design: Retrospective

Setting: King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia

Subjects: All patients diagnosed with SLE were identified, using a computerized retrieval system, for the period January 1, 2000 to May 31, 2012.

Intervention(s): Data pertaining to demographics, risk factors for cerebrovascular accident and CNS manifestations were collected from the patients’ medical charts

Main Outcome Measure(s): CNS-SLE and the predictors of death among the studied cohort

Results: The study included 307 patients (91% females) with a mean (M ± SD) age of 35.6 ±13 years and mean disease duration of 9 ± 5 years. CNS manifestations were found in 70 patients (23%). The commonest was stroke in 25 patients (35%) and aseptic meningitis, cerebritis, recurrent stroke and cavernous sinus thrombosis occurred only in one patient each (1.4%). The most significant predictors for CNS involvement were hyperlipidemia (OR = 5.48) followed by positive Antiphospholipid antibodies (OR = 2.74). By univariate analysis CNS involvement, negative anti-nuclear antibody (ANA) and combined low complements were found to be predictors of death.

Conclusions: Clinical studies have shown varying results with respect to the prevalence of CNS involvement in SLE. Antiphospholipid antibodies (APA) is a known risk factor whereas the role played by hyperlipidemia in escalating the risk of CNS involvement in SLE warrants further clinical evaluation.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem disease. Involvement of the nervous system is a common complication of SLE. It predominantly involves the central nervous system (CNS) and is also known to affect the peripheral nervous system to a lesser extent.

CNS manifestations of SLE affect patients’ physical and mental activity, and subsequently lower their life quality[1]. The prevalence of neuropsychiatric systemic lupus erythematosus (NPSLE) ranges from 14% to over 80%[2].

Although CNS-SLE is a serious complication of SLE, it is a possibly treatable illness[3]. CNS SLE manifestations can occur in isolation without the involvement of other body systems[4].

CNS-SLE manifestations range from serious presentation like acute confusional state, seizure disorder, and stroke to subtle deficits such as mild cognitive dysfunction[4,5]. The differentiation between primary NPSLE and secondary NPSLE continues to remain one of the crucial challenges in the management of SLE patients[6]. Currently, there is a dearth of scientific data pertaining to the clinical predictors of CNS-SLE[7]. However, clinical research has established the association between specific autoantibodies and CNS-SLE. In this context, the role played by antiphospholipid antibodies (APA)
in the occurrence of cerebrovascular disease (CVD) and the association of psychosis and depression with anti ribosomal P antibodies has been documented in scientific literature\cite{2-4}. The objectives of the current study were to determine the CNS manifestations of SLE and to determine the predictors of death among the studied cohort.

**PATIENTS AND METHODS**

**Patient selection and data retrieval**

This retrospective descriptive study was conducted at the King Abdulaziz university hospital (KAUH), located at Jeddah, Kingdom of Saudi Arabia (KSA). Patients with a diagnosis of SLE were identified using the computerized databases of KAUH from 01 January 2000 to 31 May 2012. Medical records of both in and out patients, coded for the diagnosis of SLE, were reviewed to ensure that patients met the criteria for the diagnosis of SLE\cite{5}. Patients with autoimmune diseases other than SLE were excluded. The study was approved by the Biomedical Ethics Research Committee at KAUH.

**Clinical and laboratory evaluation**

The following data were recorded: demographic data (age, gender, nationality), duration of disease at the time of study, major risk factors for CVD were included in our patient check list in the form of diabetes mellitus, hypertension, hyperlipidemia and smoking. CNS-SLE syndromes were reviewed based on medical records data. Given below is an explanation of the diagnostic criteria and definitions of CNS-SLE included in the current study.

All past NPSLE syndromes were listed and classified according to the standardized American College of Rheumatology (ACR) nomenclature and case definitions\cite{6,8}. Demyelinating syndrome was defined as acute or relapsing demyelinating encephalomyelitis with evidence of discrete neurologic lesions distributed in place and time\cite{7}.

The term ‘lupoid sclerosis’ has been used to describe SLE with demyelinating syndromes resembling multiple sclerosis which are a rare manifestation of SLE and are a diagnostic challenge. Whether this entity actually exist is not clear. The committee therefore, changed the definition to demyelinating syndrome with the appropriate description to enhance further research on this rare condition\cite{8}.

The diagnostic criteria for diabetes mellitus (DM) were based upon the guidelines of the American Diabetes Association (ADA)\cite{9}. The definition of hypertension (HTN) suggested in 2003 by the seventh report of the Joint National Committee (JNC 7)\cite{10} was applied in the current study. Diagnosis of hyperlipidemia was based upon the reference values followed in the United States for the ninetieth percentile for total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides and for the tenth percentile for high density lipoprotein (HDL) cholesterol\cite{11}.

APA syndrome was diagnosed based on the modified Sapporo criteria\cite{12}. Anti-double-stranded DNA autoantibodies (anti-dsDNA) test was performed using the enzyme linked immunosorbent assay (ELISA) technique (Quanta LiteTM dsDNA Kit, INOVA Diagnostic Inc, CA, USA), and it was measured in IU/ml. Based on the manufacturer’s instructions, results of anti-dsDNA tests were classified as follows: 1) Negative: If the level was between 0 - 200 IU/ml; 2) Equivocal: If the level was between 201 - 300 IU/ml; 3) Moderately positive: If the level was between 301 - 800 IU/ml; and 4) Strongly positive If the level was > 801 IU/ml. Complement components 3 and 4 (C3 and C4) were measured by nephelometry; hypocomplementemia was defined as a level below the lower normal value (C3 < 0.75 mg/l and C4 < 0.2 mg/l). There were no specific diagnostic criteria to differentiate between delirium, confusional states and encephalopathy.

Acute confusional state (ACS) was diagnosed and defined as per American Psychiatric Association’s Diagnostic and Statistical Manual, 4th edition (DSM-IV), which lists four key features that characterize delirium as follows; 1) Disturbance of consciousness with reduced ability to focus, sustain, or shift attention. 2) A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia. 3) Disturbances that develop over a short period of time (usually hours to days) and tend to fluctuate during the course of the day. 4) Evidence from the history, physical examination or laboratory findings suggestive of the fact that the disturbance is caused by a medical condition, substance intoxication, or medication side effect\cite{13}. Any possible secondary cause of ACS was considered including infection, electrolyte abnormalities, renal failure, drug effects, etc\cite{14}. Cognitive dysfunction was defined as any combination of the following; difficulty in short or long-term memory, impaired judgment and abstract thinking, aphasia, apraxia, agnosia, and personality changes\cite{15}. Psychosis was defined as impaired and bizarre thinking that often includes delusions and hallucinations\cite{16}. Mood disorders such as depressive syndromes are defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)\cite{17}. A major depressive syndrome or episode was defined as five or more of the following symptoms, for most of the day nearly every day for a minimum of two consecutive weeks; depressed mood, loss of interest or pleasure in most or all activities, insomnia or hypersomnia, change
in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, recurrent thoughts about death or suicide (at least one symptom being either depressed mood or loss of interest or pleasure). Diagnostic criteria from the DSM-IV for anxiety disorder include excessive anxiety and worry about a number of events or activities, occurring more days than not for at least six months that are out of proportion to the likelihood or impact of feared events[19].

Cerebrovascular disease (CVD) included ischemic stroke, transient ischemic attack (TIA), hemorrhagic stroke, chronic multifocal disease (recurrent or progressive neurologic deterioration attributable to CVD) and sinus thrombosis[20]. Only radiologically confirmed hemorrhagic and ischemic stroke were included. The definition of TIA was endorsed from the 2009 guidelines from the American Heart Association and American Stroke Association (AHA / ASA) which included: a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction[21]. The current study included any reported attack of seizure whether single or repeated. Epileptic seizures were defined as seizures caused by electrical hypersynchronization of neuronal networks in the cerebral cortex while epilepsy was defined as recurrent epileptic seizures due to a genetically determined or acquired brain disorder[22]. Any movement disorders and their subtypes were included in this study; chorea, ataxia, choreoathetosis, dystonia, and hemiballismus[23]. Transverse myelitis (TM) is defined as an acute inflammatory process affecting a focal area of the spinal cord and characterized clinically by acutely or sub acutely developing symptoms and signs of neurological dysfunction in motor, sensory and autonomic nerves and nerve tracts of the spinal cord[24]. The study included any documented history of headache regardless of the type or the severity. The study included the diagnosis of aseptic meningitis if it presented with symptoms, signs and laboratory evidence for meningeal inflammation with negative bacterial cultures[25].

Lupus nephritis was defined by the presence of any of the following: proteinuria, red blood cell casts, serum creatinine >120 mmol/l or estimated glomerular filtration rate (GFR) < 89 ml/min per 1.73 m² of body surface area[26]. We excluded all patients who were on dialysis. Pulmonary manifestations were either: pleurisy, pleural effusion and pericardial effusion, pneumonia, pneumonitis, pulmonary hypertension, interstitial lung disease, bronchiectasis, diaphragmatic dysfunction, pulmonary tuberculosis (TB), pulmonary embolism (PE), adult respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage (DAH), cryptogenic organizing pneumonia (COP) and pulmonary edema[27]. Skin manifestations were identified as the presence of any of the following: malar rash or photosensitivity or discoid rash[28].

**Statistical analysis**

Statistical analysis was done using statistical package for social science (SPSS software version 18). The qualitative data were presented in the form of numbers and percentages. Chi-square test was used to compare qualitative data of two groups. Yates correction was used when appropriate. Odds ratio (OR) and 95% confidence intervals (CI) were calculated to estimate the risk. The quantitative data were presented in the form of mean and standard deviation (SD). Student t test was used to compare quantitative data of two groups. Logistic regression was done to determine the predictors of death. Results with p-value less than 0.05 were considered statistically significant.

**RESULTS**

The study included 307 patients with SLE from 01 January 2000 to 31 May 2012. The study population mainly comprised of females (91%) with a mean (± SD) age of 35.6 ± 13 years and mean disease duration of 9 ± 5 years at the time of diagnosis.

CNS manifestations were found in 70 patients (23%). Stroke was the commonest manifestation, observed in 25 patients (35%). Out of these, 16 patients (64%) were cases of ischemic stroke whereas nine (36%) experienced hemorrhagic stroke. Aseptic meningitis, cerebritis, recurrent stroke and cavernous sinus thrombosis comprised the least common manifestations seen only in one patient each (1.4%) each. Table 1 summarizes the CNS manifestation in the studied population.

We tried to analyze if the presence of stroke risk factors in SLE patient with stroke have any statistical

<table>
<thead>
<tr>
<th>CNS Neuropsychiatric manifestations</th>
<th>Number of cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>Seizure</td>
<td>17</td>
<td>24.2</td>
</tr>
<tr>
<td>Acute confusional state</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal movement</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Cavernous sinus Thrombosis</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Memory disturbance</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Several features may co-exist with the same patient
significance in our study. As mentioned previously 25 patients had stroke, 19 out of 25 patients (76%) had no co-morbid illnesses. Only six patients (23%) had co-morbid illnesses which were not statistically significant risk factors for stroke development. All of the co-morbid patients were hypertensive, while three were diabetics, two were hyperlipidemic and none were smokers.

On examining the different clinical and laboratory variables for the risk of the development of any CNS manifestation, the most significant predictors were hyperlipidemia (OR = 5.48, \( p = 0.001 \)) followed by positive APA (OR = 2.74, \( p = 0.001 \)). Table 2 summarizes the association between different variables and the CNS manifestations. Other co-morbidities due to SLE did not show any statistical significance as predictors for the development of CNS-SLE apart from pulmonary involvement (\( p = 0.045 \), Table 4).

During the study period, a total of 28 patients died (9%). Out of these, 10 patients (36%) had CNS manifestations. As per univariate analysis, certain predictors of death were noted among the study patients, namely: negative ANA, low C3, CNS manifestations and combined low C3 and C4. However, as per multiple logistic regression analysis, the only significant predictor was negative ANA, CNS manifestations and low C3. On the other hand combined low C3 and C4 were found to be non-significant (Table 3). Positive APA and anti-dsDNA did not represent a significant risk for mortality.

### Table 2: Characteristics of 307 patients with SLE with and without central nervous system manifestations

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>With CNS n = 70 (%)</th>
<th>Without CNS n = 237(%)</th>
<th>p-valuea</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Mean ± SD)</td>
<td>34.84 ± 13.1</td>
<td>35.84 ± 13.66</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 30 (n = 124)</td>
<td>28 (40)</td>
<td>97(41)</td>
<td>0.99</td>
<td>0.96</td>
<td>(0.55-1.66)</td>
</tr>
<tr>
<td>More than 30 (n = 182)</td>
<td>42(60)</td>
<td>140(59)</td>
<td>1.04</td>
<td></td>
<td>(0.6-1.79)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 276)</td>
<td>64 (91)</td>
<td>212 (89)</td>
<td>1.26</td>
<td></td>
<td>(0.46-3.59)</td>
</tr>
<tr>
<td>Male (n = 31)</td>
<td>6(9)</td>
<td>25 (11)</td>
<td>0.079</td>
<td></td>
<td>(0.28-2.16)</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi (n = 170)</td>
<td>27 (39)</td>
<td>143 (60)</td>
<td>0.41</td>
<td></td>
<td>(0.23-0.69)</td>
</tr>
<tr>
<td>Non Saudi (n = 137)</td>
<td>43 (61)</td>
<td>94 (40)</td>
<td>0.002*</td>
<td>2.42</td>
<td>(1.35-4.35)</td>
</tr>
<tr>
<td>Duration of disease (Mean ± SD) Years</td>
<td>9.25 ± 6.16</td>
<td>9.36 ± 5.24</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-morbid illness (n = 58)</td>
<td>14(20)</td>
<td>44 (18.6)</td>
<td>0.92</td>
<td>1.1</td>
<td>(0.56-2.15)</td>
</tr>
<tr>
<td>Diabetes Mellitus (n = 16)</td>
<td>4 (6)</td>
<td>12 (5)</td>
<td>0.76</td>
<td>1.14</td>
<td>(0.35-3.64)</td>
</tr>
<tr>
<td>Hypertension (n = 39)</td>
<td>14 (20)</td>
<td>35 (15)</td>
<td>0.38</td>
<td>1.44</td>
<td>(0.73-2.86)</td>
</tr>
<tr>
<td>Hyperlipidemia (n = 17)</td>
<td>10 (14)</td>
<td>7 (3)</td>
<td>0.001*</td>
<td>5.48</td>
<td>(1.82-16.76)</td>
</tr>
<tr>
<td>Smoking (n = 5)</td>
<td>1 (1.4)</td>
<td>4 (1.7)</td>
<td>0.67</td>
<td>0.84</td>
<td>(1.7-7.7)</td>
</tr>
<tr>
<td>APA – positive (n = 65)</td>
<td>25(37)</td>
<td>40(21)</td>
<td>0.001*</td>
<td>2.74</td>
<td>(1.45-5.17)</td>
</tr>
<tr>
<td>Anti-dsDNA IU/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative 0 - 200 (n = 82)</td>
<td>17 (24)</td>
<td>65(27.4)</td>
<td>RC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equivocal 201-300 (n = 45)</td>
<td>9(12)</td>
<td>36(15.2)</td>
<td>0.89</td>
<td>0.96</td>
<td>(0.35-2.57)</td>
</tr>
<tr>
<td>Moderately positive 301-800 (n = 50)</td>
<td>9(12)</td>
<td>41(17)</td>
<td>0.87</td>
<td>0.84</td>
<td>(0.31-2.23)</td>
</tr>
<tr>
<td>Strongly positive &gt; 800 (n = 130)</td>
<td>35(50)</td>
<td>95(40)</td>
<td>0.39</td>
<td>1.41</td>
<td>(0.69-2.85)</td>
</tr>
<tr>
<td>Hypocomplementemia mg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3 (n = 88)</td>
<td>23(34)</td>
<td>65(30)</td>
<td>0.46</td>
<td>1.29</td>
<td>(0.7-2.39)</td>
</tr>
<tr>
<td>C4 (n = 155)</td>
<td>37(55)</td>
<td>118(55)</td>
<td>0.54</td>
<td>1.15</td>
<td>(0.69-2.03)</td>
</tr>
<tr>
<td>C3 &amp; C4 Combined (n=73)</td>
<td>21(33)</td>
<td>52(25)</td>
<td>0.21</td>
<td>1.52</td>
<td>(0.8-2.88)</td>
</tr>
</tbody>
</table>

SLE: systemic lupus erythematosis, CNS = central nervous system manifestation, APA = antiphospholipid, C = complement, RC = reference category for other variables is the negative group, OR = odds ratio, CI = confidence interval

*a Data were presented as frequencies (number and percentages) unless otherwise stated

*p-value was estimated by Chi-square, *significant association p < 0.05

### Table 3: Univariate and multivariate analysis of the death predictors among the studied patients with SLE (n = 307)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted odds ratio 95% confidence interval</th>
<th>p-value</th>
<th>Unadjusted odds ratio 95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS manifestations</td>
<td>2.39 (1.85-6.69)</td>
<td>0.075</td>
<td>2.02 (0.85-4.62)</td>
<td>0.069</td>
</tr>
<tr>
<td>Low C3</td>
<td>1.96 (0.71-16.7)</td>
<td>0.04*</td>
<td>2.229 (1-4.96)</td>
<td>0.71</td>
</tr>
<tr>
<td>Combined low C3 and C4</td>
<td>2.33(0.21-25.71)</td>
<td>0.029*</td>
<td>2.42 (1.07-5.46)</td>
<td>0.48</td>
</tr>
<tr>
<td>Negative ANA</td>
<td>15.47 (7.6-71.36)</td>
<td>0.001*</td>
<td>17.47 (7.6-71.36)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

CNS: central nervous system manifestation, ANA: antinuclear antibody, C: complement, * = statistically significant
The calculated mean of duration between the central nervous system insult in SLE patients and the time of death was 16 ± 4.4 months.

DISCUSSION

The three most important findings elicited through this study are as follows: The prevalence of CNS-SLE was determined to be 23%, the most common manifestation was stroke occurring in 35% of the patients and a significant association was noted between the occurrence of these manifestation and positive APA as well as hyperlipidemia. The presence of CNS involvement combined with low complement and negative ANA were found to be crucial predictors of CNS-SLE related mortality.

The current study is quite similar to a previous study conducted by Kasitanon et al which showed the frequency of NPSLE to be 18%.10, 28 Previous studies by Piyawan et al and Mok et al revealed a much lower frequency of CNS-NP-SLE than our study (11.3% and 13.5% retrospectively).17, 29 The current study reported a lower prevalence than the studies conducted by Ainiala et al and Brey et al which showed a frequency of 54% and 55.4% respectively.6, 20 Stroke showed the highest frequency among other CNS manifestations (35%), followed by headache (34%) and seizure (24.2%).

In the current scientific literature review, a recent study by Piyawan et al showed high prevalence of seizure (32%), CVA (23%) and Psychosis (23%). In contrast, the results of some previous SLE cohort studies6,29,31,32 showed that the CNS-SLE most commonly involved cognitive function (55 - 80%), followed by headache (24 - 72%), and psychosis (0 -8%).

In the current study, the prevalence of the ischemic subtype of stroke was found to be much higher than the hemorrhagic subtype (64% versus 36% respectively). In comparison, previous similar studies have reported only one case as recurrent ischemic stroke.33, 34 The pathogenesis of CVD in SLE is related to multifactorial processes such as accelerated atherosclerosis and a hypercoagulable state as a consequence of APA.35 Both, large or small cerebral vessels are a target for SLE.36

Headache was reported in a total of 24 out of 70 patients. However, it is noteworthy in this regard, that the causes of headache can be multifactorial. Also, it is practically difficult in a retrospective study, to prove if all cases of headache were directly related to SLE disease or not. Therefore, establishing a direct causal relationship seems difficult in this scenario.37 We could not find details about types of headache for most patients. This is a limitation of our study due to its retrospective design.

Two cases out of 70 were diagnosed as transverse myelitis, which is a well-known neurological association with SLE and may be its initial feature.38 We had one case of aseptic meningitis which may not be directly related to SLE but to the medications used in treatment, including Ibuprofen (and less commonly other non steroidal anti inflammatory drugs - NSAIDs, excluding aspirin) and azathioprine.39, ACS was reported in a total of 10 out of 70 patients (14.2%).

A high prevalence of seizures was noted in the study (24.2%). Seizures can be primarily caused by lupus or secondary to brain infection, drugs, or metabolic disturbances and hypertension.40 We had 17 / 70 patients with seizure presentation. Nine cases were generalized tonic clonic seizures, one case was a simple partial seizure, one case was partial seizure with secondary generalization, one case was complex partial seizure and one case had both types of seizures (myoclonus and generalized tonic clonic). Data was missing in five cases. Psychiatric symptoms were reported in eight patients (11%). Five cases were reported as psychosis, one case had an anxiety disorder and depression was reported in two cases.

Similar to the study conducted by Piyawan et al, this study too, did not report any case of cognitive dysfunction. Also, this study did not find any documented case of demyelinating syndrome. A variation can be seen in the prevalence of different CNS manifestations between different clinical studies. This can be attributable to multiple factors including the age of SLE onset, race, ethnicity and socio-economic status and the method of study, and can also be related to ACR nomenclature system.39

Table 4: Frequency and distribution of co-morbidities related SLE among patient with and without CNS-SLE

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>With CNS-SLE N = 70 (%)</th>
<th>Without CNS-SLE N = 237 (%)</th>
<th>p-value*</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus nephritis</td>
<td>27 (39)</td>
<td>63 (27)</td>
<td>0.06</td>
<td>1.7</td>
<td>(0.9-2.9)</td>
</tr>
<tr>
<td>Hematological abnormalities</td>
<td>8 (11)</td>
<td>21 (9)</td>
<td>0.52</td>
<td>1.3</td>
<td>(0.5-3.09)</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>21 (30)</td>
<td>44 (19)</td>
<td>0.045</td>
<td>1.8</td>
<td>(1.01-3.39)</td>
</tr>
<tr>
<td>Skin manifestation</td>
<td>15 (21)</td>
<td>56 (24)</td>
<td>0.67</td>
<td>0.8</td>
<td>(0.45-1.65)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>28(40)</td>
<td>81 (35)</td>
<td>0.41</td>
<td>1.25</td>
<td>(0.72-2.18)</td>
</tr>
</tbody>
</table>

CNS: central nervous system manifestations, SLE: central nervous system manifestation

N = 70 (%)

N = 237 (%)

*Statistically significant

95% CI: 95% confidence interval
The current study tried to elicit significant predictors for the occurrence of CNS-SLE. The findings of this study showed that the presence of ANA and antibodies to dsDNA did not correlate with CNS manifestations. The risk of CNS-SLE in APA positive patients was found to be statistically significant (p = 0.001). Although hyperlipidemia showed significant association with the development of CNS-SLE, the small number of hyperlipidemic patients in this study, limits the robustness of this result.

With respect to the prediction for stroke or other CNS-SLE, the data gathered in the current study, could not differentiate whether or not these predictors are secondary to SLE. This study did not include the control status of these diseases. However, it should be included in future studies.

The European League against Rheumatism (EULAR) recommendation suggests treatment for NPSLE with steroids, immunosuppressants, antiplatelet and anticoagulation agents. However, clear guidelines for its prevention are unavailable. Since APA and hyperlipidemia play a strong role in prediction, a physician could treat every SLE patient with an agent that may affect both. For example, the antimalarial agent hydroxychloroquine, as recent studies suggested, may act as a seroconverter of APA and may lower the lipid level.

The strength of this study is that it included a large number of SLE patients. On the other hand, the limitation of the study is its retrospective nature which might have resulted in the underestimation of some of the manifestations, specifically cognitive impairment, although it was included in the classification criteria. In addition, the onset of DM and HTN in relation to SLE onset, were not recorded. This makes it unclear whether these were a primary or secondary to SLE. The control status of the different risk factors for CVD could not be documented in this study. Hence, a prospective study has been initiated, in order to evaluate SLE patients for cognitive impairment alone, to better understand whether or not this problem has been underestimated.

CONCLUSION

Clinical studies have shown varying results with respect to the prevalence of CNS involvement in SLE. APA is a known risk factor whereas the role played by hyperlipidemia in escalating the risk of CNS involvement in SLE warrants further clinical evaluation.

ACKNOWLEDGMENT

Conflict of Interest: The authors report no conflict of interest and this research work has not been funded by any pharmaceutical company.
Original Article

A Selective Clipping Microsurgical Treatment for Multiple Intracranial Anterior Circulation Aneurysms

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Department of Neurosurgery, First Hospital of Jilin University, Changchun, China

Kuwait Medical Journal 2014; 46 (1): 21 - 27

ABSTRACT

Objective: To summarize our experiences with selective clipping microsurgical treatment and prognoses of 146 cases of intracranial multiple anterior circulation aneurysms
Design: Non-concurrent cohort study
Setting: Department of Neurosurgery, First Hospital of Jilin University, Changchun, China
Subjects and Methods: One hundred and forty-six patients with intracranial multiple anterior circulation aneurysms who underwent surgical clipping.
Intervention: These aneurysms in each patient were given selective treatment depending on whether the patients were symptomatic, or had likelihood of rupture if they were asymptomatic
Main Outcome Measures: Glasgow outcome scale (GOS) was applied to assess the patients’ condition.
Results: Among 146 patients, there were 169 asymptomatic and 146 symptomatic aneurysms. Symptomatic aneurysms included 139 ruptured and seven unruptured aneurysms. All symptomatic aneurysms were clipped, and asymptomatic aneurysms were treated selectively. A postsurgical GOS of grade 5 was found in 136 cases, grade 4 in 6 cases, grade 3 in 1 case, and grade 1 (death) occurred in 3 cases. At postsurgical follow-up, computed tomography angiography (CTA) revealed completed clipping of all symptomatic aneurysms and no changes in the asymptomatic. Apart from the three cases in which death occurred during hospitalization, we followed up a total of 128 of the remaining 143 cases between 5 and 10 years. The post-surgical mortality rate was 2.1%. Follow-up GOS scores were grade 5 in 123 patients (96.1%), grade 4 (3.1%) in four and grade 3 in one (0.8%).
Conclusions: Satisfactory prognoses were achieved in the selective treatment of intracranial multiple anterior circulation aneurysms.

INTRODUCTION

Multiple intracranial aneurysms, usually located in the anterior circulation, are common in the clinical setting[1, 2]. Treatment of such multiple aneurysms depends firstly on the selection of those symptomatic (i.e., ruptured and unruptured aneurysms causing symptoms), and secondly on the treatment of those that are asymptomatic[3-5]. Whether all multiple intracranial aneurysms need to be treated is still controversial.

Both endovascular treatments and aneurysm clipping surgery after craniotomy are effective for intracranial aneurysms[6]. Endovascular treatment makes simultaneous embolization of all aneurysms possible. Moreover, its risk is lower for the separate treatment of the symptomatic aneurysms[6, 7]. However, the risk of embolization of the asymptomatic aneurysms exists[8]. Therefore, it is unreasonable to simultaneously embolize multiple intracranial anterior circulation aneurysms, and rebleeding should be strictly avoided to ensure a favorable prognosis. The alternative is clipping surgery after craniotomy, and while this option cannot clip all aneurysms simultaneously, it is effective in the treatment of the symptomatic aneurysms. Clipping surgery after craniotomy is also more popular than endovascular treatment for economic reasons.

The above considerations make it apropos that we summarize our experiences in the microsurgical treatment of multiple intracranial aneurysms. In the present study, we retrospectively analyzed 146 cases of multiple intracranial anterior artery aneurysms treated at the First Hospital of Jilin University (northeast...
China) from January 2003 to January 2008.

PATIENTS AND METHODS

General information
We retrospectively analyzed 146 patients who had received a selective clipping microsurgical treatment for multiple anterior circulation aneurysms at the First Hospital of Jiling University (northeast China) from January 2003 to January 2008. Recruited subjects were 26.7% male and the male:female ratio was 1.27:4. Ages ranged from 27 to 75 years (mean: 52.4 years). These patients included 124 (84.9%) cases of subarachnoid hemorrhage (SAH) alone, 12 (8.2%) cases of SAH and intracerebral hematoma, 3 (2.1%) cases of SAH and intraventricular hemorrhage (IVH), and 7 (4.8%) cases of oculomotor palsy. Hunt-Hess classification at presentation was I in 98 cases, II in 13, and III in 28. The seven patients with oculomotor palsy were excluded from Hunt-Hess classification. Computed tomography angiography (CTA), digital subtraction angiography (DSA), or both, were performed to confirm the diagnosis of multiple anterior circulation aneurysms.

Selection criteria of symptomatic aneurysms
An aneurysm was deemed symptomatic if accompanied by an SAH or oculomotor palsy. An aneurysm symptomatic for an SAH met the following criteria: (a) CT images showed that the site of the SAH matched the site of the aneurysm; (b) On CTA or DSA images the body of the aneurysm appeared round or oval, or a whole aneurysm was irregular due to ruptured bleb connecting with the top of the aneurysm, and a parent artery had become thinner due to vasospasm; and (c) The volume of a ruptured aneurysm was relatively large, the longitudinal axis of the aneurysm was the same as the direction of the blood flow, and the ruptured bleb was located at the site of blood flow impact. In cases of oculomotor palsy, an aneurysm was considered symptomatic if the condition was caused by unruptured aneurysms and the aneurysms were located on the same side of an artery that lead to symptoms of oculomotor palsy.

Strategy of selective treatments
Clipping ruptured symptomatic aneurysms was the first priority for treatment. When unruptured asymptomatic aneurysms were located at the same side as the symptomatic, they were clipped or wrapped. If on the opposite side and with a diameter < 5 mm, conservative observation was applied. However, clipping surgery was performed on unruptured asymptomatic aneurysms on the opposite side of the symptomatic aneurysms if the diameter was ≥5 mm and the patient's age was < 60 years, or the size was ≥ 10 mm and the patient was < 70 years old. In all locations and for all sizes, aneurysms associated with oculomotor palsy were clipped as well.

Surgical methods
A pterional approach was taken to expose aneurysms. First the symptomatic aneurysms were clipped, and then asymptomatic aneurysms on the same side were assessed and clipped or wrapped with cotton. After clipping ruptured symptomatic aneurysms, cisternal toilette of the intracisternal clot and hematoma was meticulously performed; decompressive craniectomy was performed as necessary. For patients with severe bleeding, postoperative lumbar drainage of the cerebrospinal fluid containing the blood was performed for seven days to prevent cerebrovascular spasm. Intravenous nimodipine was administered continuously for three weeks.

Follow-up
At follow-ups three and six months after clipping surgery, CTA was performed to confirm the lack of residue or recurrence of aneurysms. Telephone follow-ups continued every six months, in which the Glasgow outcome scale (GOS) was applied to assess the patients' condition.

RESULTS

Characteristics of ruptured and unruptured multiple intracranial aneurysms
Of 146 patients, the concurrence of two anterior circulation aneurysms was found in 126 (86.3%), and 3, 4, and 5 aneurysms in 18 (12.3%), one (0.7%), and one (0.7%), respectively. Of the 146 symptomatic aneurysms, 139 (95.2%) were ruptured, and 7 (4.8%) unruptured were found with a diameter of 1 - 23 mm (average: 5 mm). We observed 169 asymptomatic aneurysms with a diameter of 0.7 - 15 mm (average 3.3 mm), including 23 with a diameter > 5 mm, and 4 with a diameter >10 mm. The data of multiple intracranial anterior circulation aneurysms in 146 patients are summarized in Table 1.

Distribution of symptomatic and asymptomatic intracranial aneurysms
Among 146 symptomatic aneurysms, 54, 42, and 36 aneurysms were found in the posterior communicating artery, the anterior communicating artery, and the middle cerebral artery bifurcation, respectively. In addition, nine were in the internal carotid artery bifurcation, two in the distal anterior cerebral artery, and one each in the anterior choroidal, distal middle cerebral, and paraclinoid arteries.

Of 169 asymptomatic aneurysms, 81 were seen in the middle cerebral artery bifurcation, 39 in the posterior communicating artery, 17 in the anterior communicating artery, nine in the internal carotid artery bifurcation, eight in the anterior choroidal artery,
six in the distal anterior communicating artery, six in the ophthalmic artery, and three in the paraclinoid artery. The data of distribution of symptomatic and asymptomatic aneurysms are summarized in Table 2.

### Results of clipping surgery

A postsurgical GOS of grade 5 was observed in 136 cases, grade 4 in six cases, grade 3 in one case, and grade 1 (death) occurred in three cases.

There were 126 cases with a concurrence of two aneurysms. Of these, 78 were located on the same side (including anterior communicating aneurysms and distal anterior cerebral aneurysms combined with other aneurysms). Clipping was always applied for symptomatic aneurysms. In 65 cases, clipping asymptomatic aneurysms was performed together with the symptomatic, which was considered the first phase in the clipping of asymptomatic aneurysms. Wrapping asymptomatic aneurysms was performed in four cases. The second phase in the surgical clipping of asymptomatic aneurysms was performed after the patient had recovered well from the first surgery; this occurred in one case. Conservative observations were made in eight cases. For the 78 cases with a concurrence of two aneurysms located on the same side, the GOS score was grade 5 in 76, and grade 4 in two.

In 48 cases with a concurrence of two aneurysms was found on both sides, and all symptomatic aneurysms in these cases were clipped. The first phase of clipping of asymptomatic aneurysms was performed in two cases, and the second phase in 12. Conservative observations were made in 34 cases. After surgery, the GOS scores for the 48 cases in which a concurrence of two aneurysms was found on both sides were grade 5 in 44 cases, grade 4 in three, and grade 3 in one.

A concurrence of three aneurysms was found in 18 cases. Eight of these involved the clipping of one aneurysm and the observation of two, and the GOS scores were grade 5 in all eight of these cases. In seven cases the clipping of two aneurysms was required and observation of one. For these seven cases, postsurgery GOS scores were grade 5 in six, and grade 4 in one. Two cases involved a first phase clipping of three aneurysms, and the GOS scores were grade 1 (the patients died of

### Table 1: Multiple intracranial anterior circulation aneurysms in 146 patients

<table>
<thead>
<tr>
<th>Sites of multiple aneurysms</th>
<th>n</th>
<th>Symptomatic (Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcomA+Bi-McA</td>
<td>29</td>
<td>AcomA (22) Bi-McA (7)</td>
</tr>
<tr>
<td>AcomA+PcomA</td>
<td>7</td>
<td>AcomA (4) PcomA (3)</td>
</tr>
<tr>
<td>AcomA+DacA</td>
<td>4</td>
<td>AcomA (3) DacA (1)</td>
</tr>
<tr>
<td>AcomA+Bi-IcA</td>
<td>4</td>
<td>AcomA (3) Bi-IcA (1)</td>
</tr>
<tr>
<td>AcomA+OphA</td>
<td>3</td>
<td>AcomA (3)</td>
</tr>
<tr>
<td>AcomA+AdhA</td>
<td>1</td>
<td>AcomA (1)</td>
</tr>
<tr>
<td>AcomA+PcA</td>
<td>1</td>
<td>AcomA (1)</td>
</tr>
<tr>
<td>B-PcomA</td>
<td>16</td>
<td>L-PcomA (9) R-PcomA(7)</td>
</tr>
<tr>
<td>PcomA+I-Bi-McA</td>
<td>13</td>
<td>PcomA (11) Bi-McA (2)</td>
</tr>
<tr>
<td>PcomA+C-Bi-McA</td>
<td>12</td>
<td>PcomA (9) Bi-McA (3)</td>
</tr>
<tr>
<td>PcomA+I-PcA</td>
<td>2</td>
<td>PcomA (1) PcA (1)</td>
</tr>
<tr>
<td>PcomA+I-AdhA</td>
<td>3</td>
<td>PcomA (3)</td>
</tr>
<tr>
<td>PcomA+C-AdhA</td>
<td>1</td>
<td>PcomA (1)</td>
</tr>
<tr>
<td>PcomA+I-Bi-IcA</td>
<td>3</td>
<td>PcomA (1) Bi-IcA (2)</td>
</tr>
<tr>
<td>PcomA+C-Bi-IcA</td>
<td>1</td>
<td>PcomA (1)</td>
</tr>
<tr>
<td>PcomA+OphA</td>
<td>1</td>
<td>PcomA (1)</td>
</tr>
<tr>
<td>B-Bi-McA</td>
<td>15</td>
<td>L-Bi-McA (10) R-Bi-McA (5)</td>
</tr>
<tr>
<td>Bif-McA+C-AchA</td>
<td>1</td>
<td>-- AchA (1)</td>
</tr>
<tr>
<td>Bif-McA+C-OphA</td>
<td>1</td>
<td>Bif-McA (1)</td>
</tr>
<tr>
<td>Bif-McA+DacA</td>
<td>2</td>
<td>Bif-McA (1) DacA (1)</td>
</tr>
<tr>
<td>Bif-McA+I-Bi-IcA</td>
<td>5</td>
<td>Bif-McA (2) Bi-IcA (5)</td>
</tr>
<tr>
<td>B-Bi-IcA</td>
<td>1</td>
<td>-- R-Bi-IcA(1)</td>
</tr>
<tr>
<td>AcomA+B-Bi-McA+B-PcomA</td>
<td>1</td>
<td>AcomA (1)</td>
</tr>
<tr>
<td>AcomA+B-Bi-McA+PcA</td>
<td>1</td>
<td>AcomA (1)</td>
</tr>
<tr>
<td>AcomA+B-Bi-McA</td>
<td>3</td>
<td>AcomA (1) Bi-McA(2)</td>
</tr>
<tr>
<td>B-Bi-McA+PcomA</td>
<td>2</td>
<td>-- Bi-McA (2)</td>
</tr>
<tr>
<td>B-Bi-McA+DmcA</td>
<td>1</td>
<td>DmcA (1)</td>
</tr>
<tr>
<td>I-PcomA+I-Bi-McA+AcomA</td>
<td>2</td>
<td>PcomA (2)</td>
</tr>
<tr>
<td>PcomA+C-Bi-McA+AcomA</td>
<td>1</td>
<td>PcomA (1)</td>
</tr>
<tr>
<td>I-PcomA+I-AdhA+AcomA</td>
<td>1</td>
<td>-- AcomA(1)</td>
</tr>
<tr>
<td>B-PcomA+AcomA</td>
<td>1</td>
<td>-- AcomA(1)</td>
</tr>
<tr>
<td>B-PcomA+DacA</td>
<td>1</td>
<td>-- PcomA (1)</td>
</tr>
<tr>
<td>B-PcomA+AdhA</td>
<td>1</td>
<td>-- PcomA (1)</td>
</tr>
<tr>
<td>B-PcomA+B-Bi-McA</td>
<td>1</td>
<td>-- PcomA (1)</td>
</tr>
<tr>
<td>I-PcomA+I-Bi-IcA</td>
<td>1</td>
<td>-- PcomA(1)</td>
</tr>
<tr>
<td>B-Bi-McA+I-DacA+C-Bi-IcA</td>
<td>1</td>
<td>-- Bi-McA(1)</td>
</tr>
<tr>
<td>Bi-IcA+C-OphA+C-Bi-McA</td>
<td>1</td>
<td>-- Bi-IcA(1)</td>
</tr>
<tr>
<td>B-Bi-IcA+I-PcomA+C-Bi-McA</td>
<td>1</td>
<td>-- Bi-IcA(1)</td>
</tr>
</tbody>
</table>

n: number of patients; B: Bilateral; L: Left; R: Right; I: Ipsilateral; C: Contralateral; AcomA: Anterior communicating artery; Bi-McA: Bifurcation-Middle cerebral artery; PcomA: Posterior communicating artery; DacA: Distal anterior cerebral artery; Bi-IcA: Bifurcation-Internal carotid artery; OphA: Ophthalmic artery; AdhA: Anterior choroidal artery; PcA: Paraclinoid carotid artery; DmcA: Distal anterior cerebral artery

### Table 2: Distribution of symptomatic and asymptomatic aneurysms

<table>
<thead>
<tr>
<th>Site of aneurysms</th>
<th>Symptomatic aneurysms n (%)</th>
<th>Asymptomatic aneurysms n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior communicating artery</td>
<td>42 (71.2)</td>
<td>17 (28.8)</td>
<td>59</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>54 (58.1)</td>
<td>39 (41.9)</td>
<td>93</td>
</tr>
<tr>
<td>Middle cerebral artery bifurcation</td>
<td>36 (30.8)</td>
<td>81 (69.2)</td>
<td>117</td>
</tr>
<tr>
<td>Internal carotid artery bifurcation</td>
<td>9 (50)</td>
<td>9 (50)</td>
<td>18</td>
</tr>
<tr>
<td>Other sites</td>
<td>5 (17.9)</td>
<td>23 (82.1)</td>
<td>28</td>
</tr>
</tbody>
</table>
cerebral infarction). Finally, in one case there was a second phase of the clipping of three aneurysms, and the GOS score was grade 5.

There were two cases of concurrence of > 3 aneurysms. One of these patients died of cerebral infarction after the simultaneous clipping of three aneurysms (GOS score was grade 1). In the other case, two aneurysms were clipped and the GOS score for both was grade 5.

### Results of follow-up

At the 3- and 6-month follow-ups, CTA images showed complete clipping of aneurysms; the symptomatic, and also the asymptomatic clipped together with the symptomatic. No residue of the necks of aneurysms was found, and no change was seen in those aneurysms receiving conservative observation. Three of the 146 patients died during the hospitalization, 143 patients survived. The post-surgical mortality rate was 2.1%. We successfully completed follow-up for 128 of the remaining 143 cases by the telephone. The follow-up time was ranging from 5 to 10 years, the last date is December 2012. Total person-years of follow-up were 972.8 person-years (mean: 7.6 years of follow-up). Follow-up GOS scores were grade 5 in 123 patients (96.1%), grade 4 (3.1%) in four and grade 3 in one (0.8%).

There were 15 cases lost to follow-up (10.5%) after the post-operative CTA examination, of whom 27% were male. Mean age of patients lost to follow-up was 51.2 years, and 13 cases (87%) had a concurrence of two aneurysms. GOS scores were grade 5 in 14 and grade 4 in one of the patients lost to follow-up. All 15 patients were lost to the follow-up after the post-operative CTA examination.

All but seven patients had a GOS grade of 5 after surgery, and continued with grade 5 throughout the period of follow-up. Table 3 presents the GOS grade of the seven patients with a GOS grade < 5 after surgery or at any time during follow-up.

### DISCUSSION

In the present study, we recruited 146 patients with multiple intracranial anterior circulation aneurysms. These patients were suitable to accept the clipping surgery with the good Hunt-Hess classification or the oculomotor palsy, whose epidemiological characteristics should be representative of those with this condition in northeast China. The ratio of male to female (1.27:4) was similar to previous reports in the literature (1.3). We found that aneurysms most often occurred in the middle cerebral artery, followed by the anterior communicating artery, the posterior communicating artery, and others. Nevertheless, the anterior communicating artery had the highest risk of rupture, followed in sequence by the posterior communicating artery, the internal carotid artery bifurcation, and the middle cerebral artery. We also found that prognosis was excellent after implementing a selective intervention algorithm for asymptomatic aneurysms (as per Komotar et al(13)), with only one rupture of an unclipped asymptomatic aneurysm during a mean of 7.6 years of follow-up.

Patients presenting with multiple intracranial aneurysms are common in clinics. Although their epidemiological characteristics change with geographic area (i.e., depending on the location of neurosurgery centers), regularities can be found(4-7). The following reports of Kaminogo et al(14) and Baumann et al(15) are two examples of relatively large scale studies of multiple intracranial aneurysms.

Kaminogo et al(14) in 2003 reported an epidemiological study of multiple intracranial aneurysms in a group of Japanese patients. The results showed that morbidity was 17.7%, and the aneurysms were more commonly seen in females over 50 years old. The ratio of male to female was 1:3. The aneurysms were often in the anterior circulation, and occurred more often in the posterior communicating artery than in the middle cerebral artery; the lowest incidence was in the anterior communicating artery. The rate of rupture of the aneurysms in the anterior communicating artery was 63.9%, which was far higher than in other arteries.

Baumann et al(15) reported in 2008 that the morbidity in a group of Swiss patients with anterior circulation aneurysms was 12-fold greater than for those with posterior circulation aneurysms. The ratio of male to female was 1:3. The lowest incidence was found in the

### Table 3: GOS grade during follow-up after surgery among seven patients with GOS less than grade 5.

<table>
<thead>
<tr>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1(GOS)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4*</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Case 2(GOS)</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Case 3(GOS)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Case 4(GOS)</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Case 5(GOS)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 6(GOS)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*GOS Score for Case 1 was reduced after hemorrhage of asymptomatic aneurysm at baseline that had not been clipped. Cases 1 and 2 had two unilateral aneurysms; cases 3 through 6 had two bilateral aneurysms; and cases 6 and 7 had three concurrent aneurysms.
posterior communicating artery. Although the rate of incidence in the middle cerebral artery was higher than that of the anterior communicating artery, the later was more prone to rupture. The rate of incidence in the anterior communicating artery was 65%.

These results are also similar to those mentioned above\textsuperscript{[14, 15]}. Based on these findings, our case study demonstrates features of clinical presentations and treatments for multiple intracranial anterior circulation aneurysms in northeast China. Although multiple intracranial anterior circulation aneurysms commonly occur in every neurosurgery center, currently no uniform guidelines are available for treatment of such aneurysms. Consequently, varied treatments are provided, based on individual clinical experience. Even if prognosis was good, quite a few problems associated with different treatments need to be resolved. For example, an identification of symptomatic aneurysms is the first issue to be considered in the treatment of multiple intracranial anterior circulation aneurysms.

Criteria given for the identification of symptomatic aneurysms in different studies seem similar, but contain subtle differences. In 1985, Nehls et al\textsuperscript{[16]} summarized eight criteria for determining the site of rupture in patients with SAH and multiple aneurysms: (1) the exclusion of extracranial artery aneurysms; (2) severity at the site of SAH; (3) angiographic signs such mass effect or local vasospasm; (4) aneurysms occupying a large area or with an irregular shape compared to others; (5) clinical signs of local neurological deficiency (such as pain, cranial nerve palsy); (6) electroencephalogram (EEG) indicating abnormal peripheral tissues around artery aneurysms; (7) progression of aneurysms during follow-up by DSA; (8) priority given to the aneurysm of higher risk when it is difficult to judge. In 2006, James\textsuperscript{[11]} established four criteria for the identification of ruptured aneurysms: (1) at the site of SAH with the most severe hemorrhage; (2) the larger aneurysm; (3) an irregular shape, and a ruptured cyst or secondary aneurysm revealed by imaging; (4) vasospasm can be seen on a parent aneurysm. The latter standard has been widely applied and is quite feasible. Current treatments of intracranial anterior circulation aneurysms mostly comply with these criteria.

In our case study, we identified and treated symptomatic aneurysms based on these criteria. Nevertheless, in addition to the criteria promoted by James et al\textsuperscript{[11]}, after summarizing our experiences in the treatment of 146 cases, we found that it is critical to consider parent aneurysms and hemodynamics as well. We found that two factors are helpful in making an efficient judgment of a rupture of an artery aneurysm: if the longitudinal axis of an aneurysm is the same as the direction of the impact of the blood flow, and the ruptured cyst is seen at the point of the impact, indicating that the aneurysm was ruptured. Based on these criteria, almost all symptomatic aneurysms were correctly assessed in our cases.

After locating the symptomatic aneurysms, specific strategies are the key for the treatment of multiple intracranial anterior circulation aneurysms. We reviewed the literature regarding treatments of multiple intracranial anterior circulation aneurysms, and found that strategies for treatments have evolved over time. The earlier reports advocated that, besides clipping symptomatic aneurysms, the others should be clipped as well to prevent life-threatening conditions due to rupture and hemorrhage. For example, Vajda et al\textsuperscript{[17]} in 1986 and Orz et al\textsuperscript{[18]} in 1996 reported 138 and 221 cases of multiple intracranial aneurysms, respectively, and treatments were provided for almost all of the aneurysms with successful outcomes. Besides craniotomy clipping surgery, endovascular embolization was applied in a group of 38 patients by Solander et al\textsuperscript{[19]} in 1999, and good outcomes were achieved as well\textsuperscript{[19]}. Nagagara et al\textsuperscript{[20]} in 2010 systematically evaluated endovascular treatment of unruptured artery aneurysms in a meta-analysis, and suggested that this treatment was safe. However, comparative evaluation of outcome and follow-up were not made.

Although successful outcomes were reported in these studies, the risks associated with simultaneous treatment of symptomatic and asymptomatic aneurysms is much higher than that of symptomatic aneurysms and selective treatment of the asymptomatic. Currently, with the better understanding of the natural course of intracranial unruptured aneurysms, clipping all unruptured aneurysms is not suggested. For example, based on the international subarachnoid hemorrhage test (ISAT) published in 2003, follow-up observations should be made for unruptured aneurysms < 7 mm in diameter, and particularly for patients without SAH history and with only a 0.15% chance of hemorrhage\textsuperscript{[20, 21]}. Thus, unruptured asymptomatic aneurysms among multiple intracranial aneurysms should be given selective treatment. In our cases, we selectively provided treatment for 146 patients with multiple intracranial anterior circulation aneurysms in northeast China. In either the first or the second phases of clipping surgery, we treated symptomatic aneurysms and only those asymptomatic that carried a high rupture risk. Nevertheless, we achieved a better outcome.

In the present study, we did not choose ISAT criteria for unruptured symptomatic aneurysms, but instead referred to the criteria proposed by Komotar et al\textsuperscript{[12]} in 2008, i.e., conservative observation for unruptured aneurysms < 5 mm and patients < 60 years old, or clipping surgery for unruptured aneurysms > 10 mm and patient age < 70 years old. These criteria were
based on a systematic analysis of unruptured artery aneurysms that included ISAT and were developed by statistical analysis. If a diameter of 5 mm is the criterion, the risk of rupture of aneurysms is lower than that of 7 mm, and moreover the risk of treatment is acceptable.

In the present retrospective of craniotomy clipping surgeries for aneurysms performed during Jan 2003-Jan 2008, we analyzed 146 cases which had met the criteria for treatment. Apart from the death of three patients, we followed-up 128 cases between 5 and 10 years postsurgery. In these, hemorrhage occurred in only one case in which asymptomatic aneurysms had not been treated, six years postsurgery. Therefore, overall outcome of treatment was satisfactory. In addition, the risk of rupture of asymptomatic aneurysms with a diameter < 5 mm during conservative observation was only 0.78%, which was consistent with previous studies[10, 22]. It appears that satisfactory prognosis is achievable when the criterion for craniotomy clipping surgery of intracranial asymptomatic aneurysms is set at a diameter < 5 mm. Although in the present study we maintained conservative observation for aneurysms < 5 mm, when asymptomatic and symptomatic aneurysms were located on the same side, we evaluated the asymptomatic aneurysms and wrapped them if clipping was unnecessary.

In the studies by Vajda et al[17], Orz et al[18], and Solander et al[19], all aneurysms were treated and good outcomes were achieved, and Wachter et al[4] reported that simultaneous treatment of multiple intracranial aneurysms did not aggravate vasospasms. However, these results were mostly obtained from simultaneous clipping of two aneurysms. In our cases, prognosis was good when two aneurysms on the same side were simultaneously clipped, but the clipping of three aneurysms on the same side resulted in poor prognosis and postsurgical cerebral infarction. This suggests that careful considerations should be made before clipping three aneurysms on the same side, to prevent serious consequences.

CONCLUSION

In summary, satisfactory prognosis can be achieved by careful selective clipping of multiple intracranial anterior circulation aneurysms. Treatment of symptomatic aneurysms is the priority. When asymptomatic aneurysms are on the same side as the symptomatic, the exploration of asymptomatic aneurysms should be performed while symptomatic ones are being clipped. Whereas, when asymptomatic aneurysms are on the opposite side, the first or second phases of clipping surgery should be employed for those of diameters > 5 mm. Conservative observation and follow-up are recommended for asymptomatic aneurysms < 5 mm, and caution should be exercised to the simultaneous clipping of three aneurysms on the same side, to prevent poor prognosis.

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REFERENCES

Original Article

Discharge against Medical Advice among Children Admitted into Pediatric Wards at Al-Jahra Hospital, Kuwait

Victor Abd El Malek, Shanti Alexander, Fahed Al Anezi
Department of Pediatrics, Al-Jahra Hospital, Kuwait

Kuwait Medical Journal 2014; 46 (1): 28 - 31

ABSTRACT

Objective: To determine the prevalence of pediatric discharge against medical advice (DAMA) in our society, reasons if present, common diagnosis and severity of illness of patients availing DAMA

Design: Retrospective study

Setting: Department of Pediatrics, Al-Jahra Hospital, Kuwait

Subjects: Children aged one day to 12 years who were subjected to DAMA from the pediatric wards during the period, January to June 2012

Intervention: The relevant required data from these children’s files were collected and analyzed

Main Outcome Measure: The frequency of DAMA in our community and the factors responsible

Results: The prevalence of DAMA was 8.49%. 56% out of them left the hospital within 24 hours of admission. There was no seasonal variation and no significant difference between general and subspecialty wards. Infants constituted the largest group of DAMA cases (55.5%). Male Kuwaiti children represent the biggest group among DAMA cases. The reasons for DAMA, as reported in the patient’s files were: dissatisfaction with the treatment (38%), domestic obligations and inconvenience of hospitalization (31%), perception that the child was well enough to leave hospital (21%), inadequate facilities in the hospital for their children (8%), extended length of stay(2%). The most common diagnosis among our DAMA cases was respiratory and gastro-intestinal illnesses (31% and 25% respectively).

Conclusions: We had a high prevalence of DAMA. There was increased prevalence of DAMA cases among Kuwaiti nationality, infants and male patients. Improvement of parent-pediatrician relationship, health awareness and provision of day care services may decrease the overall incidence of DAMA.

KEY WORDS: day care services, discharge against medical advice (DAMA), Kuwait, parent–pediatrician relationship

INTRODUCTION

The phenomenon of discharge of hospitalized children against medical advice (DAMA) is a serious public health issue. It prevents the patients from maximally utilizing the benefits of the services rendered by the health facility\(^\text{[1-2]}\). This decision made by the parents may have an important influence on the outcome of the illness of their children\(^\text{[3]}\). It has the potential of increasing not only the child’s morbidity and mortality, but also, in many cases, the long term sequelae\(^\text{[4-5]}\). Such discharges are also known to be distressing to the attending pediatrician and other health care professionals involved in the care of these children\(^\text{[6]}\).

The prevalence of DAMA which has been reported among hospitalized children varies from 1.2% to 31% depending on the population studied\(^\text{[7-8]}\). Although DAMA occurs both in developed and developing countries, the reasons may be different\(^\text{[9-10]}\). Various studies have shown that financial constraint is the major determinant of DAMA\(^\text{[8-11]}\). The majority of published studies on DAMA have focused on adult patients\(^\text{[6,12]}\). Few studies have been published regarding DAMA among the pediatric population\(^\text{[13-14]}\).

The present study sought to determine the prevalence of pediatric DAMA in our society, reasons if present, common diagnosis of the patients discharged DAMA and the seriousness of these discharged patients. The knowledge obtained could help health care administrators in formulating policies aimed at minimizing its frequency and thereby improve health care delivery to these children.

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SUBJECTS AND METHOD

This retrospective study was conducted in the Pediatric Department of Al-Jahra Hospital, Kuwait. Al Jahra hospital is a government hospital under the Ministry of Health, located at the centre of Jahra city. The hospital has a total capacity of 753 beds including 148 in the pediatric department. This hospital provides medical services to a population of more than 463,000 people. Most of the medical services offered are free for all patients.

The pediatric department consists of an inpatient section, an outpatient section and an emergency unit. The inpatient section of the pediatric department consists of two general wards (ward 7 and 28), three sub-specialty wards (ward 6 - metabolic diseases, ward 8 - nephrology and ward 31 - neurology) and a pediatric intensive care unit (PICU). Patients between the age of newborn and 12 years are accepted for admission.

The admission registers of the five pediatric wards were reviewed and DAMA cases from 1st January, 2012 to 30th June, 2012, were reviewed and the relevant information collected from their files and recorded. The recorded information includes the personal data of the patient (age, sex and nationality), and the date and time of discharge. For purpose of analysis, the morning shift was considered between 8 am – 2 pm and the duty shift between 2 pm – 8 am next day. The main diagnosis, as well as the reason for DAMA was noted. The subset of DAMA patients who stayed for less than one day was analyzed in detail. The data obtained was tabled, analyzed and illustrated.

RESULTS

During the six months’ period of the study, a total of 5,391 children were admitted to the five pediatric wards. The total number of DAMA cases during the same period was 458. The prevalence of DAMA was 8.49 % out of the total admissions. The majority of them (66%) were discharged during the duty shift. 65% of our DAMA patients were discharged during the week day compared to 35% during the weekend. The average number of patients going DAMA on a working day was 65% divided by five working days giving a value of 13%. This is less in comparison to the average DAMA on a weekend with 35% divided by two weekend days giving a value of 17.5%). Thus, there was an increase in the percentage of DAMA cases over the weekends as compared to weekdays.

It was observed that there was a seasonal decrease in the total number of admissions to the pediatric wards from January to June. Despite this, the absolute number of patients taking DAMA remained relatively constant throughout the study period. The percentage of DAMA patients when compared to the total admissions was lowest in the month of March (7.2%) and highest in the month of June (12%), (Fig. 1).

The distribution of admission and DAMA cases among the five pediatric wards, revealed that the highest rate of DAMA cases were in ward 28 (general ward), then ward 31 (neurology sub-specialty) followed by ward 7 (another general ward), then ward 8 (nephrology) and ward 6 (metabolic diseases ward) respectively.

The gender ratio among the DAMA cases was 58.3% male to 41.7% female. Kuwaiti nationals constituted 59% of patients taking DAMA.

Among different age groups, infants were the largest group with 55.5% of DAMA cases. Children beyond infancy and less than six years old constituted 32% of cases. Neonates as a group represented 17.5% of the total cases (Fig. 2).

The reasons for DAMA were documented in 41% of all the files reviewed and the reasons were reported as follows: parental dissatisfaction with the treatment (38%), domestic obligations and inconvenience of hospitalization (31%), perception that the child was well enough to leave hospital (21%), inadequate facilities in the hospital for their children, including lack of sufficient resting areas (8%), extended length of stay (2%).
It was found that 56% of the DAMA patients left the hospital within 24 hours of admission. 71% of these were discharged during the duty shift (2 pm to 8 am).

The commonly reported diagnosis among the DAMA patients was respiratory cases (31%) followed by gastro-intestinal cases (25%). Other reported diagnosis in decreasing order of frequency were fever without focus for investigation, CNS diseases, accidental drug or toxin ingestion, miscellaneous, blood transfusions in chronic hemolytic anemias, genitourinary cases, sedation for procedure cases and cardiac patients. The morbidity pattern of admitted patients to our pediatric department during the same period was found as the following: respiratory cases (30.7%), gastro-intestinal cases (27%), febrile convulsion and CNS cases (9%) followed by urinary tract diseases, heart diseases, then miscellaneous diagnosis in decreasing order of frequency.

DISCUSSION

The phenomenon of discharge against medical advice among pediatric patients has a serious hidden health problem. The health care provider is caught in between respect for the parent's decision and their desire to provide complete care for the patient.

The DAMA rates vary between countries and even within a country. The rate of DAMA is always less in advanced countries[8,10]. Lower rates of DAMA indicate better health services. The rate of DAMA in our community is relatively high (8.49%) compared to other similar communities like Qatar which has less than 1%[14]. The consequences of DAMA on morbidity and mortality are well-documented[4]. The observed re-admission rates are high from 20.7% to 24.5% with children often coming with complications due to delayed / missed medical care[15]. There is a variation in the rate of DAMA between different months. However, this does not reflect any particular season. Relatively higher rate of DAMA during the weekends is a general phenomenon. This can be attributed to overcrowding and shortage of staff during these periods. However, the apparent higher rate of DAMA during the duty time (2 pm to 8 am) is false. When we calculated the percentage of patients who availed of DAMA per hour, we realized that 34 % of patients who availed it during the morning shift of 6 hours accounted to a much higher rate (5.8%) compared to the apparent higher rate of 66 % in the duty shift, which actually gives a much lower rate (3.6%). Thus, the number of DAMA cases are not related to the duty shifts (duration of the duty shift is 18 hrs). There was no difference in the incidence of DAMA between a general ward and a specialty ward. The pediatricians in the department are rotated between different wards on a monthly basis to save any bias of having certain staff being fixed for some wards.

Infants constituted the largest group of DAMA cases (55.5 %), which put them as a group at higher risk of morbidity and mortality. Similar conclusion was found by Abdulateef et al in Qatar (90%) and Roland et al in Nigeria (52.5%)[13,15]. Male Kuwaiti children represent the biggest group among DAMA cases. This could be explained by the tradition of giving more importance to males in the community.

A lack of proper understanding by the parents of their child’s condition and dissatisfaction of the medical services rendered to them was a major reason for DAMA in our study. This can be solved partially by more effective doctor-parental interaction.

Financial constraint was the most reported reason for DAMA all over the world[8,16,17]. This does not apply to our community as most of the medical services in this hospital are free. However, this has led to some unforeseen drawbacks such as continuous overcrowding which leads to relative inadequacy of the available facilities for the children and their families. Subsequently, many parents would prefer to opt for paid private medical services as they would be getting better facilities. Providing greater facilities at the hospital would help in addressing this problem.

21 % of our DAMA discharges were due to the parental perception that their child was well and fit for discharge. This can be attributed to a lack of understanding of the patients’ parents about their diseases process and treatment. It can be managed by improved doctor-parent interaction and health awareness.

The reasons for DAMA reported in our study were dissatisfaction with the treatment, domestic obligations and inconvenience of hospitalization, perception that the child was well enough to leave hospital, inadequate facilities in the hospital for the children and families including lack of sufficient resting areas, and extended length of stay. These were similar to the studies from other parts of the world with the exception of financial constraints, although the order of importance may have been different[11,14,15].

The most common diagnosis among our DAMA cases was respiratory and gastro-intestinal diseases. This is similar in order of frequency to the general causes of admission in our population. This was different from the data collected from other countries. Ikefuna et al found that septicemia was the commonest cause of DAMA in Nigeria (25.4%)[10]. Roodpeyma et al reported neonatal jaundice as the most frequent cause in Iran (37.1%)[16]. This reflects the common causes of hospital admission in our community. The high prevalence of respiratory diseases among our community can be due to the high percentage of children having bronchial asthma, extensive use of air conditioners, presence of frequent dust storms in this
desert community, extensive smoking among people including indoor smoking and environmental pollution by the oil refineries. The incidence of gastro-intestinal cases in the community can be substantially decreased by improving health awareness and through active management by parents along with the pediatricians on an outpatient basis.

56% of the DAMA patients had left the hospital within 24 hours of admission. This could be explained by the fact that the parents were not adequately counseled by the pediatricians before admitting patients. These can be handled by more effective interaction by the staff with the parents. This would support the suggestion that opening of day care service units with special consideration for gastro-intestinal and respiratory problems may be beneficial to the patient in terms of providing appropriate medical services which may be of duration of less than 24 hours.

This study has the following limitations: Firstly, the low percentage of documentation of the reason for DAMA by the discharging pediatrician in the medical record and secondly, the parents may not have communicated the genuine reason for DAMA to the pediatrician on direct questioning, as compared to an anonymous questionnaire otherwise.

CONCLUSION

The discharge against medical advice among pediatric patients is a serious hidden health problem affecting both the children and health services. We had a high prevalence of DAMA in our community. This mandates further studies. In this study, it was found that DAMA cases were more prevalent among Kuwaiti nationality, infants and male patients. The majority of them left before completing 24 hours in the hospital. The cardinal reasons for DAMA were parental dissatisfaction with the treatment, domestic obligations, perception that the child was well enough to leave hospital, inadequate facilities in the hospital and lack of sufficient resting areas and prolonged length of stay. Also, it was found that the most common diagnosis reported among our DAMA cases were respiratory and gastro-intestinal illnesses. Improvement in parent-pediatrician relationship, health awareness and, providing day care services may improve the overall percentage.

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REFERENCES

Original Article

Protective Effects of 5-Aminosalicylic Acid on Acrylamide Toxicity in the Testis and Blood Leukocytes of the Rat

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ABSTRACT

Objectives: Acrylamide (AA) has many applications in the chemical industry. It has been shown to be a reproductive toxicant in animals and is associated with risk of cancer. The objective of this study was to investigate the protective effect of 5-aminosalicylic acid (5-ASA) against AA induced testicular and geno-toxicity.

Design: Experimental study

Setting: King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia

Intervention: Animals were orally gavaged with AA at a dose of 45 mg/kg/day for five consecutive days and 5-ASA was injected concomitantly at two different doses, 25 and 50 mg/kg/day.

Main Outcome Measures: Effect on epididymal sperm count, on histological changes in the testis, on COMET assay in blood leukocytes, on serum testosterone level and on CYP2E1 expression in liver and testis (S9) fractions.

Results: COMET assay undertaken on blood leukocytes showed geno-toxicity in the form of COMET cells with increased tail movement, while ELISA of serum testosterone showed severe reduction in testosterone level, which was reversed by concomitant 5-ASA treatment. ELISA of CYP2E1 showed a two-fold higher concentration in control liver S9 when compared to control testis S9. 5-ASA (50 mg/kg) induced the level of liver CYP2E1, potentially increasing AA metabolism and clearance. Light microscopy examination showed multinucleated giant cells and tubular atrophy in the testis after AA treatment.

Conclusion: At the used dose, AA caused toxic effects in male rat that can be reduced by concomitant treatment with 5-ASA, which might be considered as an antidote to AA toxicity in victims of AA poisoning.

KEY WORDS: acrylamide, 5-ASA, COMETs, CYP2E1, testosterone

INTRODUCTION

Acrylamide (AA) is an important compound in the production of polyacrylamide which is used in a variety of industries. Polyacrylamides are used in sewage treatment and potable water treatment and purification, paper industry, petroleum industry to enhance oil recovery and greatly used for chromatography and electrophoresis in experimental research. AA monomer is also used in the production of grouts and soil stabilizers.

Acrylamide has also been considered as “probably carcinogenic to humans” by the International Agency for Research on Cancer (IARC). It is well known as a neurotoxicant after human and animal exposure. In rat and mice studies, the no observable effect level (NOEL) for neurotoxic effect has been reported to be between 0.2-10 mg/kg body wt/day, and this is far above dietary exposure. It has also been shown to elicit reproductive toxicity in laboratory animals.

In a recent study conducted by Kermanl-Alghoraishi et al., AA has been reported to affect the membrane integrity of epididymal spermatozoa in mice. It also decreased sperm vitality and caused abnormal motility in a sub-chronic study conducted by Song et al. In rat, AA was shown to affect the normal development of the sperm, significantly affect hind limb motor coordination and directly damage Leydig cells. Several lines of evidence suggest that AA biological activity is
mainly due to addition with protein, while its primary activity with DNA is alkylation, mainly due to its active metabolite glycidamide[6]. The two main metabolic pathways that have been elucidated for AA metabolism are glutathione conjugation[7,8] and epoxidation to glycidamide (GA)[8,9]. Many studies have reported on the role of cytochrome P450 in the metabolism of AA, in particular cytochrome P450 2E1[10,11]. Recently, human CYP2E1 was reported to mediate the formation of glycidamide from AA[12]. AA was proposed to cause the release of free radicals, which decrease the oxidative defense system in the cell, leading to the development of cancer[13,14]. Taken together, it is therefore important to identify protective applications against the actions of AA, both to prevent immediate and long-term damage from low-level environmental exposures and in victims of AA poisoning. 5-ASA has been reported previously to have a potent antioxidant and anti-inflammatory activity which were proposed to be due to inhibition of prostaglandin synthase and/or lipoxygenase activities[15]. In addition, ASA has been shown to improve semen characteristics and restore fertility in patients with ulcerative colitis who suffered from infertility after long-term treatment with sulfasalazine (SSZ)[16]. Also, pretreatment of endosulfan treated rats with 5-ASA, significantly reduced sperm shape abnormalities, with histopathological analysis of seminiferous tubules and Leydig cells indicating significant protection from endosulfan induced tissue damage[17]. Taken together, these two last pieces of data are strongly supportive that 5-ASA is able to protect the testes from ROS-mediated damage, as occurs during AA toxicity. It was therefore hypothesized that 5-ASA could have a protective role in AA-induced reproductive toxicity in male rats. Therefore, the major aim of this study was to investigate the potential protective effects of 5-ASA on AA-induced testicular and geno-toxicity.

MATERIALS AND METHODS

General Materials

Plus One™ AA (PAGE grade, purity > 99.95 %, < 0.05% impurities of acryl acid) was obtained from Pharmacia Biotech (Upsala, Sweden) and 5-ASA 95% was obtained from Sigma-Aldrich (Steinheim, Germany). Testosterone ELISA kit was purchased from Alpico Diagnostics™ (Windham, USA) and rat cytochrome P450 2E1 ELISA kit was obtained from USCLNLF™ (Wuhan, China). All other chemicals and materials were purchased from BHD laboratory supplies (Analar®, England) and were of molecular biology grade.

Animals and Dosage Formulation

This was an experimental study in which a total of 30 virgin male Sprague-Dawley rats were used. Rats were purchased from King Fahad Medical Research Center (KFMRC) in Jeddah, KSA, and allowed to acclimatize in the experimental environment for three days before dosing initiation. They were housed 4-5 per polycarbonate cage with wood shaving as bedding. Animals were maintained under controlled environment at 22 ± 2°C and relative humidity of 40 - 65% and 12 hrs / 12 hrs light / dark cycles throughout the experimental period. The rats were fed laboratory chow, which was supplied by Grain Silos and Flour Mills Organization (Jeddah, KSA). Tap water in plastic bottles with steel sipper tubes were used for an adlibitum supply of water.

Rats were six weeks old and weighed 203 - 231 gm. The dose of AA used to produce testicular damage was 45 mg/kg/day; although this dose was above the daily dietary exposure (of AA) it was reported previously to induce a testicular toxicity with minimal neuro-behavioral changes. It was effective in eliciting a strong testicular and geno-toxic response over a short period of time to be able to study the mechanism of AA-induced reproductive toxicity and to investigate the protective effect of 5-ASA. The dosing solutions were freshly prepared daily using distilled water. 5-ASA was injected at two different doses, 25 and 50 mg/kg, as a freshly prepared suspension in 10% gum acacia. The control group was gavaged with 1 ml of distilled water.

Study Design

The study was conducted with five treatment groups and one vehicle control group, with five randomly chosen animals in each group (n = 5). Animals were orally gavaged with 1 ml of 45 mg/kg acrylamide, using a metallic needle curved-ball ended (size PS-20) to induce testicular damage. Concomitantly rats were treated with 1 ml of 5-ASA via intraperitoneal injection. The rats were exposed to AA and 5-ASA for five consecutive days. All groups were observed for mortality or any behavioral changes once daily during the dosing period. Animal body weight, water and food consumption were measured twice during the experiment. After five days of exposure, 3 ml of blood was collected from retro-orbital sinus in plain tubes, and then the rats were killed by cervical dislocation under ether anesthesia. One milliliter of blood was collected in EDTA tube for COMET assay. The right testis of all animals were isolated and weighed for further experimental evaluation.

All experiments were undertaken with the consent of the animal ethics committee in accordance with the guidelines set out by the Canadian Animal Care.

Methods

Preparation of hepatic and testicular S9 fractions

Preparation of liver and testes microsomal supernatant S9, was achieved according to the method of Loannides
and Parke\textsuperscript{[18]}. Animals were sacrificed by cervical dislocation under ether anesthesia. The liver and testes were immediately excised and placed in tubes immersed in ice until sacrificing all animals, provided that all steps were carried out at 4°C and using cold solutions. Organs were rinsed immediately in ice-cold 1.15% (w/v) freshly prepared KCl to remove excess blood and were blotted dry before weighing. Organs were scissor minced in a small volume of KCl (less than the total required to produce 25% and 35% suspension) to produce coarse homogenate. After that the coarse homogenates were transferred to a motor driven potter Elvehjem homogenizer using a Teflon pestle (B. Braun Melsungen AG, Germany). The tissues were homogenized on ice keeping homogenization to the minimum required to produce a smooth homogenate. Small bursts were applied to prevent heat build-up. Extra KCl was added as required to allow full homogenization without exceeding the target suspension percentage. Then the homogenates were adjusted to a 25% suspension for the liver and 35% suspension for the testes by using ice-cold 1.15% (w/v) KCl. Then the homogenates were centrifuged at 9000 g for 20 min at 4°C using a high speed centrifuge (Sigma, 3K18-Germany) to remove debris, nuclei, mitochondria and lysosomes. The supernatant (S9, microsomal supernatant) was decanted and aliquots inserted into 1.5 ml tubes and stored at -80°C until required.

Protein concentration in (S9) was determined by Total Protein method (TP method) which is a modification of the biuret reaction\textsuperscript{[19]}. The whole procedure was automatically performed using Dade Behring Dimension clinical chemistry system (USA).

Estimation of CYP2E1 concentration in testis and liver S9 fractions by ELISA

All reagents and standards were prepared and reconstituted according to the product protocol. After producing serial dilutions (10, 5, 2.5, 1.25, 0.625, and 0.312) from the undiluted standard (20 ng/ml), where the sample diluent serves as the zero standard and the undiluted standard serves as the highest concentration (20 ng/ml) of the CYP2E1. The undiluted standard is recombinant rat CYP2E1, produced by USCNLIFE\textsuperscript{TM} Co. (China) from where the kit was purchased. 100 µl of all standards, and samples were loaded to the assay plate. After 2 h of incubation at 37°C, the liquid was removed from each well without washing, One hundred microliters of detection reagent-A working solution were added to each well and the plate was incubated for 1 h at 37°C. Then each well was aspirated and washed three times by the kit washing solution using an automatic microplate washer (ELX50, Biotek-USA). After this washing step, the plate was inverted and blotted against clean paper towels. Then 100 µl of detection reagent-B working solution were added to each well, covered with the plate sealer and incubated for another 1 h at 37°C. After a further five times aspiration / wash step for all wells, 90 µl of substrate solution was added to each well, the plate was covered and incubated for 30 minutes at 37 °C under light protection. Finally 50 µl of stop solution were added to each well and the absorbance (optical density) of the stopped reaction mixture of all wells was measured at 450 nm using a multiwell microplate reader (ELX-800, Biotek-USA). For the results calculation the duplicate readings for each standard were averaged and the average zero standard optical density was subtracted from all results (standards and samples). A calibration curve was obtained by plotting the mean absorbance for each calibrator (X-axis) against the known concentrations (Y-axis) of rat CYP2E1 and the best fit line through the points on the graph was determined by regression analysis using Microsoft Office, Excel-2007. Samples CYP2E1 concentrations were determined from the calibration curve in ng/ml. The measured data were analyzed by One-way Analysis of Variance (ANOVA) and a p-value of $< 0.05$ was used as the criterion for statistical significance.

Caudal Sperm Count: Two µl from each caudal tissue suspension (diluted 1:20) was taken, and sperm number was manually counted using a Makler Counting Chamber (Sefi Medical Instruments), in a strip of ten squares. In case of oligosperma 3 - 4 strips were counted and their mean was used. The resultant number was multiplied by the dilution factor (20) and this represented their concentration in millions/ml of suspension. Counting was undertaken using a LEICA, DM 1000 light microscope at X 20 magnification.

Preparation of testsis for histological examination: The organs were initially fixed in Boun’s solution (75 ml saturated aqueous picric acid, 25 ml of 40% formaldehyde and 5 ml glacial acetic acid), for one hour and then removed for preliminary cutting. Tissues were further fixed for another 24h in 10% neutral buffered formalin\textsuperscript{[20]}. Following fixation, tissues were then processed using standard laboratory procedures for histology. Briefly tissues were embedded in paraffin blocks, sectioned perpendicular to the longest axis of the testis at approximately 3-5µm thickness and stained with Hematoxylin & Eosin. Stained sections were mounted with dextran-plasticizer xylene (DPX) and were examined using light microscopy (LEICA, DM1000) at the indicated magnification and representative images were photographed with a Leica DC -180 camera.

Single cell gel electrophoresis (COMET assay): Alkaline comet assay was performed according to the protocol of Hartmann et al\textsuperscript{[21]}, and was analyzed using Loa’s Comet Assay Software with extended dynamic range imaging (EDRI). A total of 2 µl of whole blood taken from the rats, initially collected in EDTA tubes,
was mixed with 100 µL of 1% (low melting point) agarose, after it was cooled to 37°C. Plating of 75µL of agarose mixture was performed in a dimmed light using Trevigen comet slides, which are specially treated to promote adherence of low melting point agarose, then slides were placed on ice for 8 minutes to allow agarose to solidify. After that, a gentle cell lysis was performed by immersing the slides in cold lysis buffer (2.5M NaCl, 100 mM EDTA, 10 mM Tris base, 1% sodium lauryl sarcosinate, pH 10 and 1% Triton X-100 and 10% DMSO added just before use) for 30 - 60 minutes at 4°C. The excess buffer was tapped off the slides and they were immersed in freshly prepared alkaline solution, (300 mM NaOH pellets and 1mM EDTA, pH 14 and allowed to cool before use) for 20 - 60 minutes at room temperature in the dark, to unwind the DNA and hydrolyze sites of damage, and then slides were removed from the alkaline solution with gentle removal of excess buffer as before. Slides were then transferred to a horizontal electrophoresis apparatus (CH420, UK) and alkaline solution added. Electrophoresis was conducted for 20 minutes at 1volt / cm, 300 mA, in an ice bath and under dim light to minimize light induced DNA breaks. Finally after gentle removal of excess electrophoresis solution, the slides were placed in Tris buffer (pH 7) for 10 minutes to neutralize alkali, and then immersed in absolute ethanol for five minutes to complete precipitation of DNA and accelerate dehydration. Slides were then drained, air dried, and then stained with 1µg/ml of ethidium bromide for five minutes, followed by washing for five minutes with distilled water. Analysis of comet tail was done by Loa’s single gel comet assay software with EDRI and observed with fluorescent microscope, Olympus, BX-51(Japan). Positive control used in this assay was glycidamide (from LKT laboratories, USA). It was reconstituted with distilled water. For preparation of negative control, control rat whole blood was used, alkaline comet assay was performed, and the average tail movement was calculated. For the preparation of different glycidamide dilutions (0.025 - 10mM), glycidamide was incubated with the whole rat blood for four hours at 37º C and then alkaline comet assay was performed, and analysis of comet tail was done. The percentage of cell viability and comet cells were calculated.

Testosterone ELISA assay: Direct quantitative determination of free testosterone in rat serum was performed by using an ELISA kit for competitive enzyme immunoassay. All reagents were prepared and / or reconstituted according to the product protocol. A total of 25 µl of each ready to use calibrators or standards with the following approximate concentrations (0, 0.35, 1.45, 7.2, 30, and 150 pg/ml - they contain free testosterone in a serum based buffer with a non-mercury preservative); the kit control (7.1pg/ml); and the serum samples were dispensed onto a 96-well anti-free testosterone antibody coated micro-well plate. Then 100 µl of the conjugate working solution (free testosterone horseradish peroxidase conjugate) was added into each well and gently mixed for 10 seconds followed by incubation at 37 ºC for one hour. Wells were then washed three times with wash buffer (buffer with a non-ionic detergent and a non-mercury preservative) using an automatic micro plate washer (ELX50, Biotek-USA) that dispensed 300 µl of wash solution per well per cycle. Excess wash solution was removed and the total of 150 µl of TMB substrate (tetramethyl benzidine and hydrogen peroxide in a DMSO-containing buffer) was then added to each well. After 10-15 minutes incubation at 37 ºC the reaction was stopped with the addition of 50 µl/well of stopping solution (1 M sulfuric acid). The optical density (450 nm) of each well was subsequently measured with multi-well micro-plate reader (ELX800, Biotek-USA). The mean absorbance for each standard was calculated and calibration curve plotted on semi-log paper with the mean optical density on the Y-axis and the calibrator concentrations on the X-axis and the values of the unknown samples were read directly from the curve.

Statistical analysis: Differences between obtained values (mean ±SD) were compared by one-way analysis of variance (ANOVA), using Graph Pad Prism & Graph Pad Instat, followed by Tukey-Kramer multiple comparison test. A p-value less than 0.05 were used as the criterion for a statistically significant difference.

Ethical committee approval
The research was approved by the Biomedical Ethics Research committee in the Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

RESULTS
Effects of ASA on AA induced changes in epididymal sperm count
Rats treated with AA (45 mg/kg/day) showed significant reduction in sperm count in comparison to normal control group (Fig.1, p < 0.05), as was expected. However, no statistically significant change in epididymal sperm count was detected for rats treated with AA and both doses of ASA when compared to AA control group which suggested that both doses of ASA on this five days duration exposure could not protect rats from the toxic effects of AA on total sperm count. As indicated ASA (25 or 50 mg/kg) was administered by IP injection concomitantly with oral gavage of AA treatment, with gum acacia as a solvent.
luminal sperm reserve. Also, there was a clear cellular differentiation starting with the spermatogonia from the basement membrane and ending at the lumen with the spermatozoa. In addition rats treated with 5-ASA and gum acacia showed normal testes, (Fig. 2A, B).

As (Fig. 3A) from control rat testis showed normal testis histology, evidence of morphological changes in the testicular histology was observed in the AA-treated rats, including germ cell degeneration and atrophy to the seminiferous epithelium of rat testis, with disruption in the normal looking appearance of the testis. In addition, a reduction in the luminal sperm reserve was observed, and in many tubules vacuolations were observed in-between cells of seminiferous tubule (Fig. 3B). Co-treatment of rats with AA and 25 mg/kg 5-ASA, did not completely remove the acrylamide-induced testicular changes, but the observed damage

Histopathology

In the control group seminiferous tubules and spermatogenesis appeared normal with apparent

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**Fig. 1:** Total sperm count per gram of cauda after AA and ASA treatment. (Data were expressed as mean ± SD, n = 5). The symbol represents statistical significance (ANOVA) from normal control: *p < 0.05*, followed by Tukey-Kramer multiple comparison test. The AA + ASA groups were compared to AA control.

**Fig. 2:** Representative light microscopy of transverse sections of testes isolated from: (A) control, (B) 50 mg/kg ASA. Rats were treated for 5 consecutive days. All show testes with normal histology. Sections stained with H&E stain and viewed using light microscopy.

**Fig. 3:** Representative light microscopy of transverse sections for general architecture of testes, indicating the AA toxicity and the protective effect of ASA, isolated from control, AA and ASA treated rats. (A) Shows testis isolated from control rat. (B) Shows testis of AA (45 mg/kg)treated rat, with disruption in normal histological appearance of the tubules with germ cell degeneration and reduction in sperm reserve with multiple vacuoles of different size (see arrows).
was generally less, with a significantly less damage to the germ cell population in most of the tubules, although there were still areas of damage (Fig. 3C).

Interestingly, AA-treated rats exposed to a dose of 50 mg/kg 5-ASA, appeared to be almost completely protected from the AA-mediated toxicity, with nearly normal histological appearance of the testis. Normal spermatogenesis was observed, with no multinucleated giant cells, no vacuolations, and no tubular atrophy (Fig. 3D).

![Fig. 3](image1.png)

Fig. 3: (C) Shows the mild protective effect of ASA at a dose of 25 mg/kg on the testicular toxicity caused by AA, note the slight restoration of normal histological structure of the testis with increased sperm reserve in the lumen of the tubule with some residual damage in the form of atrophy and germ cell degeneration.

(D) Shows the strong protective effect of ASA at a dose of 50 mg/kg on the testicular toxicity caused by AA, the tubules almost appearing normal with normal histology and restoration of luminal sperm reserve with normal germ cells. Sections stained with H&E stain and viewed using light microscopy.

As shown in (Fig. 4A) from control rat testis, Leydig cells showed normal histology and color intensity. However with acrylamide treatment (Fig. 4B) Leydig cells showed severe atrophy and degeneration with reduction in size, numbers of cells and color intensity. Importantly, at the dose of 25 mg/l kg lday ASA, (Fig. 4C) and at the dose of 50 mg/kg/day (Fig. 4D) of ASA, appeared to strongly prevent the Leydig cell

![Fig. 4](image2.png)

Fig. 4: Representative light microscopy of transverse sections for Leydig cells of the testes, indicating the AA toxicity and the protective effect of ASA on these cells. (A) Shows Leydig cells from control rat testis, with normal histology and color intensity, (B) Shows Leydig cells from AA (45 mg/kg) treated rat testis with severe atrophy and reduction in color intensity, (C) Shows Leydig cells from rat treated with AA and ASA at a dose of 25 mg/kg, indicating the protective action of ASA on AA induced toxicity on Leydig cells. Note the normal appearance of cells with increase in cells number and color intensity.
atrophy detected with acrylamide treatment, because Leydig cells appeared normal in these groups of rats.

It should be noted that at both doses of ASA protection was not complete, as some of the tubules still appeared abnormal compared to control. However, the protective effect of the 50 mg/kg of ASA was generally, more clear than with the dose of 25 mg/kg ASA. However, recovery at both doses of 5-ASA was not complete at this five-days duration of experiment.

COMET assay in peripheral blood leukocytes

In the control group, group treated with 5-ASA, and gum acacia group the measured tail movement was (0.00 - 0.001) (Fig. 5A, B, C), which is consistent with a very low level of DNA damage. In comparison, the group treated with 45 mg/kg AA (Fig. 6A) demonstrated 8.3% olive shape COMET cells, (tail movement 37.5 - 44), indicative of massive levels of DNA damage. Co-treatment with 25 mg/kg ASA (Fig. 6B), demonstrated 8.2% COMET cells and dramatically reduced the tail movement of the detected COMET to (0.8 - 1.0), with no further protection observed with the higher ASA dose treatment (50 mg/kg, Fig. 6C).

Effects of ASA on AA induced changes in serum testosterone level

As expected, a significant reduction in blood testosterone level was detected in rats treated with 45 mg/kg AA when compared to the normal control group, with no statistically significant differences detected between the control group and AA + ASA treated group. Further, there was a statistically significant increase in the level of circulating testosterone hormone among the AA plus ASA (25 or 50 mg/kg) treated rats when compared to AA control group (Fig. 7). Once again, ASA co-treatment appeared to prevent AA toxicity. This suggests that the suppressive effect of AA on circulating testosterone levels can be ablated by concomitant ASA treatment.
ROS and the CYP2E1-catalysed metabolism of AA to the reactive molecule glycidamide\textsuperscript{[22,23]}. A calibration curve was constructed from mean absorbance versus concentration, using the least square regression equation with correlation coefficients ($r^2$) routinely $\sim$ greater than 0.999. As shown in (Fig. 8A), CYP2E1 is expressed in the S9 fraction from control rats liver at a higher concentration (0.44 ng/mg protein) than in the control testis (0.074 ng/mg protein) (Fig. 8B), which is perhaps not surprising, given the important role of the liver in xenobiotic metabolism. However, whereas, AA caused a significant reduction in CYP2E1 (p < 0.01) levels in the liver when compared to the normal control, the impact of AA- treatment was the reverse in the testes when compared to the control, with CYP2E1 concentrations increased up to two-fold when compared to the normal control in the testis. It should be noted that the decrease in CYP2E1 levels in the liver was not due to liver weight changes, because no significant difference was detected in liver weight between all groups, with mean liver weight of 9.77gm (Fig. 9).

In the liver, co-treatment of AA-treated rats with ASA at a dose of 25 mg/kg/day for five days does not show any significant difference when compared to AA control group. However, at a dose of 50 mg/kg ASA there was a significant increase (p < 0.01) in the level of CYP2E1 when compared to AA control group, which indicates the strong reversing action of this higher dose of ASA on acrylamide effect on CYP2E1 level in the liver, with increasing rate of AA metabolism. This

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Effect of AA and ASA on CYP2E1 expression in liver and testis S9 fractions

CYP2E1 has been linked to the mechanism of AA-mediated toxicity, due to both the ability of this enzyme to readily become uncoupled and produce the reactive molecule glycidamide. A calibration curve was constructed from mean absorbance versus concentration, using the least square regression equation with correlation coefficients ($r^2$) routinely $\sim$ greater than 0.999. As shown in (Fig. 8A), CYP2E1 is expressed in the S9 fraction from control rats liver at a higher concentration (0.44 ng/mg protein) than in the control testis (0.074 ng/mg protein) (Fig. 8B), which is perhaps not surprising, given the important role of the liver in xenobiotic metabolism. However, whereas, AA caused a significant reduction in CYP2E1 (p < 0.01) levels in the liver when compared to the normal control, the impact of AA- treatment was the reverse in the testes when compared to the control, with CYP2E1 concentrations increased up to two-fold when compared to the normal control in the testis. It should be noted that the decrease in CYP2E1 levels in the liver was not due to liver weight changes, because no significant difference was detected in liver weight between all groups, with mean liver weight of 9.77gm (Fig. 9).

In the liver, co-treatment of AA-treated rats with ASA at a dose of 25 mg/kg/day for five days does not show any significant difference when compared to AA control group. However, at a dose of 50 mg/kg ASA there was a significant increase (p < 0.01) in the level of CYP2E1 when compared to AA control group, which indicates the strong reversing action of this higher dose of ASA on acrylamide effect on CYP2E1 level in the liver, with increasing rate of AA metabolism. This

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**Fig. 7:** Modulatory effect of ASA on serum testosterone concentration in AA-treated rats. Data were expressed as mean ± SD, n = 5. The symbol represents statistical significance (ANOVA) from normal control: ***, p < 0.001, followed by Tukey-Kramer multiple comparison test. The letter (a) represents statistical significance (ANOVA) from AA control, p < 0.01 and (b) represents statistical significance (ANOVA) from AA control, p < 0.001.

**Fig. 8:** CYP2E1 concentration in liver (A) and testis (B) S9, following AA and ASA treatment in rat, as detected by ELISA. Acrylamide was administered by oral gavage at a dose of 45 mg/kg/day for 5 consecutive days to adult male rats. Data are expressed as mean ± SD, n = 5. The symbol represents statistical significance (ANOVA) from normal control: **, p < 0.01, followed by Tukey-Kramer multiple comparison test. The letter (a) represents no statistical significance from AA control and (b) represents statistical significance (ANOVA) from AA control, p < 0.01.
is again consistent with the hypothesis that ASA can protect the rat body from the toxic effects of AA, and expands this to include other organs than the testes, such as the liver.

In the testis, AA exposure caused induction of CYP2E1 (p < 0.01) when compared to normal control. In addition, exposing AA treated rats to two different doses of ASA does not show any significant difference from AA control group in the testis.

**DISCUSSION**

In this study the potential role of the antioxidant 5-ASA in protection of AA-induced reproductive toxicity following a sub-acute exposure to AA was evaluated in rats. Concomitant treatment of 5-ASA with acrylamide was effective in preventing AA-mediated suppression in the blood testosterone level at both examined doses of ASA. In addition, ASA co-treatment improved the histological appearance of the testis, reduced the tail movement in the detected COMET cells in the blood, and suppressed CYP2E1 induction in the liver.

The result of this study indicate that, while a significant reduction was found between the 45 mg/kg AA group and the normal control with respect to sperm count per cauda, there was no significant difference from AA control group at both tested ASA doses. The result of the current study was consistent with the observed effects of ASA in ulcerative colitis patients\(^\text{[24]}\), which reported a reduction in total sperm count in patients suffering from ulcerative colitis. After changing treatment from sulphasalazine to 5-ASA, some improvement in spermatozoa function was noted, resulting in an improvement of fertility

in those patients. Further O'Marain et al.\(^\text{[25]}\) reported that 13 slow acetylator patients had significantly lower sperm counts (6.3 x 10⁶) and motility than 9-fast acetylator patients (41.2 x 10⁶). Importantly, these data also support the idea that the protective effect of ASA against testicular toxins is applicable to both humans and the model system used herein (i.e., rats).

In contrast, other investigators\(^\text{[17]}\) reported a significant increase in total sperm count at (25 and 50 mg/kg) of 5-ASA as compared with endosulfan (7.5 mg/kg) alone, which was documented previously to cause a reduction in total sperm count. However, in the previous study, 5-ASA at a dose of 25 mg/kg for 10 days was reported to improve sperm counts more than at a dose of 50 mg/kg without complete recovery. This improvement in sperm count after a high dose of 5-ASA could be due to the established antiprostaglandin-like activity of ASA, as was reported by Moskov et al., and indeed ASA has been suggested as a potential treatment in some cases of unexplained oligospermia, as sperm improvement has been observed after antiprostaglandin therapy.\(^\text{[26]}\) In the current study the reason for the lack of significant effect of ASA on AA-treated rats with respect to sperm count / cauda, could be due to dose, or short duration of exposure to ASA.

A striking feature of this study was the effect of 45 mg/kg AA on serum testosterone concentrations when compared to the normal control. In the current study, blood was taken 24h after the last dose, and the result showed that there was a very significant reduction in blood testosterone level following treatment with 45 mg/kg AA. The reduction in serum testosterone following AA exposure is consistent with the reports of Yang et al., who demonstrated a significant reduction in testosterone concentration by using radioimmunoassay, in sera of AA-treated rats at a dose of 30, 45, and 60 mg/kg/day for five days followed by three days of observation.\(^\text{[27]}\) Moreover, testosterone concentration in the culture medium of Leydig cells after incubation for 24h, decreased significantly in all AA-treated groups, indicating that testosterone reduction was due to influence of acrylamide, presumably caused by the observed dose-dependent Leydig cell death.\(^\text{[27]}\) As a result of increased Leydig cell death, testosterone level in the testis is likely to be decreased, resulting in a reduction in spermatogenesis. The result of the current study further showed that both doses of ASA can cause significant increase in the level of circulating testosterone level when compared to the AA control, which indicated that 5-ASA was successful at antagonizing the toxic effect of AA in reducing testosterone concentration in serum. In contrast, another study reported that 5-ASA could cause a reduction in the level of testosterone, when 7.5 mg/kg endosulfan was given to the rats for 10 days, during which testosterone was significantly increased.
but this was not recovered following an additional 10 days treatment with 25 mg/kg ASA. It was stated by the authors that the mechanism by which 5-ASA causes a reduction in testosterone level is not clear, although it is not clear if this is really a case of ASA causing a reduction, or failing to prevent the endosulfan-mediated reduction\textsuperscript{19}. The powerful antioxidant capacity of 5-ASA exerted on the Leydig cells, could be the cause of its influence on testosterone level, as it was reported previously that Leydig cell atrophy and death could be the cause of testosterone reduction in AA-treated rats\textsuperscript{27}.

Further\textsuperscript{28,29}, it was reported that 7, 12-dimethylbenz(a)anthracene and many other polycyclic aromatic hydrocarbons are metabolically activated to active metabolites in rat Leydig cells. Also, CYP2E1 is documented to have a role in the metabolic activation of various toxicants and carcinogens such as benzene, styrene, acrylonitrile, vinyl carbamate and many other halogenated hydrocarbon compounds\textsuperscript{30}. Taken together, these data suggest that CYP2E1 expressed in Leydig cells, will potentiate the toxicity of these compounds with increasing their active toxic metabolites with excessive release of free radicals, causing increased oxidative stress in the Leydig cells. Hence, the antioxidant activity of ASA might improve the Leydig cell toxicity after AA treatment leading to increased testosterone level.

The result of the current study indicated that AA at a dose level of 45 mg/kg causes histopathological changes in the testis of the rats. These include tubule disruption, reduction in the luminal sperm reserve, shedding of normal germinal epithelium in the lumen of the seminiferous tubules, maturation arrest in some tubules and multinucleated giant cells with vacuolations in between inner cells of the tubules. Histopathological changes in rat testis after AA treatment were well-documented previously by Yang et al\textsuperscript{22,23} and the results of this work supports these studies. AA treated rats co-exposed to 25 mg/kg ASA showed signs of repair with significant increase in germ cell population in most of the tubules, compared to AA alone, although the recovery was far from complete. This result is in agreement with Jaiswal et al, study\textsuperscript{17}. When male rats were exposed to endosulfan, together with a dose of 25 mg/kg of 5-ASA in a preventive study the rats showed signs of recovery and improvement in spermatogenesis. In the current study, the dose of 50 mg/kg of 5-ASA was much better in reducing the signs of AA-induced toxicity than with the dose of 25 mg/kg of 5-ASA, although at both dose levels of 5-ASA the recovery was not complete. This protective action of 5-ASA on AA induced histopathological changes might be due its antioxidant power to inhibit oxidative damage which depends on its ability to scavenge free radicals and by acting as a chain-breaking antioxidant with interference with the initiation and progression of lipid peroxidation\textsuperscript{27}. Its antiprostaglandin property might improve signs of the accompanying inflammatory process as well. As a result, an improvement in intratubular testosterone levels could result, leading to an improvement on spermatogenesis. Another important factor that improves testosterone levels is the effect of 5-ASA on Leydig cell atrophy. AA causes atrophy of these cells with reduction in serum testosterone level. 5-ASA prevents Leydig cell atrophy and hence maintains normal testosterone level which results in normal spermatogenesis.

This work showed the tremendous effect of 5-ASA on COMETs produced by AA in blood lymphocytes. ASA co-treatment results in dramatic reduction in COMETs tail movement, which indicates a reduction in genotoxic damage. Our hypothesis was that AA and not glycidamide is responsible for reproductive and genotoxicity. For this reason, any compound that causes increase in AA metabolism will improve the level of genotoxicity produced by AA. In this study 5-ASA has been shown to exert an induction effect on CYP2E1 expression, which results in an improvement in the level of genotoxicity when compared to the group that received AA alone. Moreover, as free radicals produced by AA may impair DNA repair\textsuperscript{33}, oxidation is an important mechanism of cell damage, which initiates a chain-reaction of lipid peroxidation that will spread through the membrane causing cleavage of unsaturated fatty acids and alteration of integral protein function leading to cell dysfunction and death\textsuperscript{33}. 5-ASA acts as a free radical scavenger\textsuperscript{34}, which characterizes its powerful antioxidant property, and leads to the beneficial effects observed when it is concomitantly given with AA.

A novel finding of the current study was the effect of 5-ASA on CYP2E1 induction in liver and testis. The results showed that CYP2E1 is normally present in the testes (0.074 ng/mg protein) with lower amount than the liver (0.44 ng/mg protein); further, this study demonstrated for the first time, that 5-ASA at the dose of 50 mg/kg caused a significant elevation (induction) of CYP2E1 in the liver when compared to AA control. Also AA caused a significant reduction in enzyme level when compared to the normal control, while in the testis AA caused significant increase in CYP2E1 level when compared to the normal control. These findings were highly consistent with the report of Jiang\textsuperscript{33}, who identified the presence of CYP2E1 mRNA in rat prostate and testis, by reverse transcription PCR, southern blotting and DNA sequencing. From the immunoblotting result, P4502E1 appears to be present in very low amounts in the testis. The contents of P450 2E1 in testicular microsomal fractions were determined to be 0.12 pmol /mg protein which increases > 2-fold (0.25 pmol /mg protein) after pyridine treatment, which
was used as an enzyme inducer. It is well documented that the expression of CYP2E1 is highest in the liver, mainly found in the endoplasmic reticulum. However it is present in small amounts in non-hepatic tissues such as kidney, nasal mucosa, lung, ovaries, testis, small intestine, colon, umbilical vein endothelial cells, lymphocytes and the brain\textsuperscript{[36]} This finding is of considerable potential importance, because it probably explains to a large extent the genotoxic insult produced in rat testis following AA treatment. While the physiological significance of P450 2E1 in testis remains unclear, the induction of this enzyme in testis might have important implications in testicular toxicity and function\textsuperscript{[17]}. CYP2E1 metabolizes a wide variety of chemicals with different structures such as small and hydrophobic compounds, including potential carcinogens\textsuperscript{[35]}. For this reason, the presence and inducibility of CYP2E1 in the testis may be of significance in the bioactivation of environmental chemicals to genotoxic metabolites. Based on the well-known and documented role of CYP2E1 in epoxidation of AA to its active metabolite glycidamide\textsuperscript{[10,20]}, as a consequence of the presence of CYP2E1 in testis, despite the apparently low level of expression, enhanced P4502E1 mediated metabolic activation in testes by exposure to inducers that are environmental pollutants such as AA, may influence adverse effects on spermatogenesis and hence on reproduction\textsuperscript{[35]}. The result of the present study hints that glycidamide is not only formed mainly in the liver by CYP2E1 and transferred by the blood to testis, but it also formed locally in the testis in small amounts.

However, during this study the concomitant treatment of AA-treated rats with the dose of 50 mg/kg 5-ASA, higher level of CYP2E1 was detected in the liver when compared to AA control, which indicated that 5-ASA can induce CYP2E1 in the liver and (might be due to protein stabilization) as a consequence, increases rate of AA metabolism with less ROS formation. Due to antioxidant property of ASA, the formed glycidamide will further be metabolized to inactive form and then excreted causing less genotoxicity and less damaging effect. This was clearly observed in this study on COMETs produced by AA in peripheral blood lymphocytes, and histopathology in the testes. In contrast, in the group exposed to AA alone, they showed significant reduction in CYP2E1 level in liver. The interpretation is that as the level of CYP2E1 in the liver is not impressively high compared to some other P450 isozymes\textsuperscript{[30]}, this large dose of AA over five days of treatment might cause partial depletion of this enzyme with significant reduction in its level in the liver. Another explanation is that AA itself may cause inhibition of the enzyme it induced and this needs further investigations. However in the testis, normally the amount of the expressed CYP2E1 is less than that in the liver. Therefore, it remains high because the major part of the given AA is metabolized by CYP2E1 in the liver and the small part of AA transferred to testis acts as an enzyme inducer but it does not cause depletion of the enzyme as in the liver. The mechanism by which 5-ASA exerts its effect in inducing CYP2E1 in the liver is not entirely clear at the moment. However, it seems likely that the antioxidant property of 5-ASA is the reason behind the reduced toxicity seen after ASA treatment. Induction of CYP2E1 is also very effective in generating reactive oxygen intermediates such as superoxide radical and H$_2$O$_2$\textsuperscript{[37]}. Thus, ASA seems to cause induction of CYP2E1 and hence increased AA metabolism with minimum ROS formation that reduces the AA testicular and genotoxicity.

**CONCLUSION**

5-ASA has been shown to protect partially or completely AA-treated rats from the severe testicular and genotoxicity resulting from AA treatment. Both doses of 5-ASA were effective in reducing COMETs in peripheral blood leukocytes. The most striking result of this study was the ability of 5-ASA to cause induction of CYP2E1 in liver and the effect of 5-ASA in reversing atrophy of Leydig cells in the testis. This impacts eventually, on the testosterone level. Further studies on AA and 5-ASA are needed to explore further molecular mechanisms involved in 5-ASA protection against AA testicular toxicity in rats.

**ACKNOWLEDGMENT**

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

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Original Article

Use of Proton Pump Inhibitors Correlates with Increased Risk of Pancreatic Cancer: A Case-Control Study in Taiwan

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ABSTRACT

Objective: To investigate whether use of proton pump inhibitors (PPIs) enhances the risk of pancreatic cancer
Design: Retrospective case control study
Settings: Department of Public Health, China Medical University, Taiwan
Subjects: We identified 977 patients aged 20 years or older with newly diagnosed pancreatic cancer as the case group between 2000 and 2010. The control group consisted of 3908 subjects without pancreatic cancer selected from the same sample.
Intervention: Use of Proton pump inhibitors

Main Outcome Measure: History of using PPIs and other comorbidities were compared between cases and controls

Results: After adjustment for confounders, multivariable logistic regression analysis showed that pancreatic cancer had strong association with PPIs use (OR 9.28, 95% CI 7.77 - 11.08). Among PPI drugs, those using esomeprazole were at the highest risk with an odds ratio of 12.1 (95% CI 9.76 - 15.0).

Conclusions: Taking PPIs correlates with increased risk of pancreatic cancer. The risk may greater for those taking esomeprazole.

KEYWORDS: pancreatic cancer; proton pump inhibitor

INTRODUCTION

Pancreatic cancer is an important global burden of cancer because of low survival rate. Among cancer related deaths, it is the eighth most common cause of death (266,000 deaths, 3.5% of the total) worldwide, the fourth in the US and the eighth in Taiwan[1-3]. The etiology of pancreatic cancer remains unclear. Studies have implicated smoking, drinking alcohol, consuming coffee, obesity, family history, medications and pancreatitis as factors associated with this disease[4-6]. Lowenfels et al in an European international cohort study found that the incidence ratio of pancreatic cancer in patients with pancreatitis was 26.3 times higher than expected[4]. A recent study found the risk of pancreatic cancer increased in patients with gastric ulcer[7].

Proton pump inhibitors (PPIs), a class of drugs that reduce gastric acid secretion, are commonly prescribed to manage peptic ulcer diseases. Their long-term effects on cancer risk have been widely discussed. Long-term omeprazole treatment may lead to hypergastrinemia and profound hypochlorhydria in response to the reduced gastric acid secretion[8,9]. Hypergastrinemia is found to be associated with digestive tract malignancies[8,10-12]. The earlier experimental studies have identified gastrin receptors in human pancreatic cancer cells, and gastrin can stimulate the growth of human pancreatic cancer cells in culture[12,13]. Thus, we hypothesized that use of PPIs may lead to hypergastrinemia, which might correlate with increased risk of pancreatic cancer. To date, no evidence is available about the role of PPIs on pancreatic cancer risk in Taiwan. Therefore, we conducted a case-control study to explore whether there is an association between PPIs use and pancreatic cancer risk.

MATERIALS AND METHODS

Study population

This case-control study used the claims data of the National Health Insurance of Taiwan. The program
has been detailed in previous studies[15-17]. In brief, this universal insurance program has a coverage rate of more than 99% in this country[17]. The database consists of a random sample with 1,000,000 insured persons, being established by the Taiwan National Health Research Institute. The database included information on insured demographic status, ambulatory care and inpatient care, and medicine prescribed. International Classification of Diseases (ICD) 9th Revision-Clinical Modification (ICD-9) was used to identify diagnosis. Data files can be linked with scrambled identification to secure privacy of patients.

Inclusion criteria
First, during the period of 2000 - 2010, subjects aged 20 years or older who had newly diagnosed pancreatic cancer were defined as the study cases (based on ICD-9 codes 157). A total of 977 cases were selected as the case group. Second, for each pancreatic cancer case, four subjects without pancreatic cancer from the same database were randomly selected as the study controls (case / control ratio = 1:4). A total of 3908 subjects were selected as the control group. Both groups were matched by gender, age (per 5 years) and index year of diagnosing pancreatic cancer. The date of diagnosing pancreatic cancer was defined as the index date. Subjects with pancreatic cancer or any other cancer (ICD-9 codes 140 - 208) before index date were excluded.

Exposure definition
Patients with early-undiagnosed pancreatic cancer initially presenting with abdominal symptoms might have been treated with PPIs. To reduce misclassification, cases receiving the PPIs therapy only within two years before the index date were excluded from the data analyses. In order to explore the effect of medications on pancreatic cancer risk, histamine-2 receptor antagonists, statins, non-statin lipid-lowering drugs, aspirin, other non-steroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors before index date were included.

Co-morbidities potentially associated with pancreatic cancer risk
Co-morbidities before index date potentially associated with pancreatic cancer risk were as follows: acute pancreatitis, chronic pancreatitis, diabetes...
mellitus, obesity, gallstones, and hepatitis C infection. All were identified with ICD-9 codes.

**Statistical analysis**

Data analysis first compared between cases and controls for distribution of demographic status, comorbidities and medications received. The Chi-square test and t-test were used to examine the differences. Only the factors found significant in the crude analysis were further included in multivariable logistic regression analysis to estimate odds ratio (OR) and 95% confidence interval (CI) for pancreatic cancer. The risk of the cancer was estimated by individual PPI with the adjustment of acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, histamine-2 receptor antagonists, statins, non-statin lipid-lowering drugs, and both of aspirin and cyclooxygenase-2 inhibitors. A p-value < 0.05 was considered statistically significant (SAS software version 9.1, SAS Institute Inc., Cary, North Carolina, USA).

**RESULTS**

**Characteristics of the study population**

There were 977 patients with pancreatic cancer as cases and 3908 subjects without pancreatic cancer as controls. Table 1 shows that the case group had higher proportions of acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, PPIs use, histamine-2 receptor antagonists use, statins use, non-statin lipid-lowering drugs use, and cyclooxygenase-2 inhibitors use. The mean duration of using PPIs was longer in case group than in the control group (9.50 Vs 4.45 months, p-value < 0.0001). Because more than 98% of subjects in both groups had used other non-steroidal anti-inflammatory drugs, these drugs were excluded from further analysis (data not shown).

**Association between co-morbidities, medications and pancreatic cancer risk**

After adjustment for multiple confounders that were found significant in the crude analysis, multivariable logistic regression analysis showed that the adjusted OR of pancreatic cancer was 9.28 for the group with PPIs use (95% CI 7.77, 11.08), as compared to the group with non-use of PPIs. In addition, acute pancreatitis (OR 16.32, 95% CI 10.24, 26.02), chronic pancreatitis (OR 2.27, 95% CI 1.00, 5.15), diabetes mellitus (OR 1.54, 95% CI 1.27, 1.87), obesity (OR 2.59, 95% CI 1.54, 4.36), and use of histamine-2 receptor antagonists (OR 1.90, 95% CI 1.53, 2.35), were significantly associated with pancreatic cancer risk (Table 2).

**Sub-analysis of association between individual proton pump inhibitors and pancreatic cancer risk**

In sub-analysis, use of omeprazole (OR 7.88, 95% CI 5.46, 11.4), pantoprazole (OR 10.9, 95% CI 8.61, 13.9), lansoprazole (OR 10.4, 95% CI 7.78, 13.9), rabeprazole (OR 8.71, 95% CI 6.28, 12.1), or esomeprazole (OR 12.1, 95% CI 9.76, 15.0), could be associated with increased risk of pancreatic cancer (Table 3).

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<th>Variables</th>
<th>Crude OR (95%) CI</th>
<th>Adjusted† OR (95%) CI</th>
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<td>Age (per one year)</td>
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<tr>
<td>Cyclooxygenase-2 inhibitors only</td>
<td>2.20 (1.79, 2.70)</td>
<td>1.04 (0.81, 1.34)</td>
</tr>
<tr>
<td>Both of above</td>
<td>2.39 (1.98, 2.89)</td>
<td>0.83 (0.65, 1.06)</td>
</tr>
</tbody>
</table>

† Adjusted for acute pancreatitis, chronic pancreatitis, diabetes mellitus, obesity, and histamine-2 receptor antagonists, statins, non-statin lipid-lowering drugs, and both of aspirin and cyclooxygenase-2 inhibitors. OR = odds ratio, CI = confidence interval.
DISCUSSION
So far, only one observational study with large sample size from UK general practice research database (GPRD) has reported that PPIs use was not associated with pancreatic cancer risk (OR 1.02, 95% CI 0.85-1.22), no matter what the duration or dosage had been[13]. Because some subjects might have underlying early-undiagnosed pancreatic cancer who initially presented with abdominal symptoms and received PPIs treatment, to reduce this confounding effect, subjects who have used PPIs only within two years before index date were excluded from this present study. In the present study, we found that the overall risk of pancreatic cancer might be increased up to 9-fold among PPIs-users. To date, only few studies can be referenced. Therefore, we cannot provide a plausible explanation about the strong discrepancies of the above results. The postulated pathophysiological basis linking hypergastrinemia and pancreatic cancer is that there are gastrin receptors in human pancreatic cancer cells, and gastrin can stimulate the growth of human pancreatic cancer cells in culture[13,14]. Additionally, bacterial overgrowth and generation of nitrosamines secondary to gastric acid suppression may also contribute to human pancreatic carcinogenesis in vitro[15]. Therefore, our finding is compatible with the prior hypothesis that use of PPIs might cause hypergastrinemia and gastric acid suppression, which might correlate with increased risk of pancreatic cancer. Nevertheless, one point needs to be discussed. Because of the lag time between diagnosing date of pancreatic cancer and onset of pancreatic cancer, we could not make sure whether PPIs use was before or after onset of pancreatic cancer, even though subjects who have used PPIs only within two years before index date were excluded from the analysis. Thus, whether PPIs use is really causality for pancreatic cancer risk or only a coincidence for treating abdominal symptoms of early-undiagnosed pancreatic cancer cannot be determined in this present study.

Some limitations should be discussed. First, there was no record of body mass index due to inherited limitation of this database. Thus, we defined obesity by using ICD-9 codes. This could lead to underestimation of the prevalence of obesity. Second, because there is no other study supporting such an association between PPIs use and pancreatic cancer, interpretation of our findings should be careful. Third, it is not clear whether our findings can be extrapolated to a Caucasian population.

CONCLUSION
We conclude that although residual confounding may have affected the results, PPIs use is associated with a markedly increased risk of pancreatic cancer in Taiwan. Further studies are needed to confirm the role of PPIs on pancreatic cancer risk.

ACKNOWLEDGEMENTS
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Conflict of Interest Statement: The authors disclose no conflicts of interest

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Original Article

Demographic Pattern and Clinical Features of Patients with Carpal Tunnel Syndrome Presenting to Orthopedic Outpatient Clinics in a Military Hospital in Kuwait

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ABSTRACT

Objectives: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. Our aim was to provide data about the demographic pattern and clinical features of this syndrome among patients in Kuwait, and compare it to data from other countries.

Design: Retrospective review of patients’ medical records

Setting: Jaber Al-Ahmad Armed Forces hospital, Kuwait

Subjects and Methods: A retrospective review of the medical records of 175 Kuwaiti patients diagnosed with CTS at Jaber Al-Ahmad Armed Forces hospital in Kuwait between January 2006 and December 2010 was done. The diagnosis was based on history, physical examination and electrodiagnostic studies. Results are presented using frequencies and percentages.

Main Outcome Measures: Demographic and clinical features of patients with CTS

Results: Out of the 175 cases, 132 (75.4%) were females, with a male to female ratio of 1:3.1. The mean age was 43.68 years (range 25 - 70 years), peaking between 46 to 50 years (40; 22.9%). All the patients complained of nocturnal symptoms, while 173 (98.3%) had daytime symptoms. Physical examination revealed abnormal sensation, positive Phalen’s test, positive Tinel sign, thenar muscle wasting and decreased power of thenar muscles in 150 (85.7%), 161 (92.0%), 129 (73.7%), 17 (9.7%) and 91 (52.0%) patients respectively. Involvement was bilateral in 141 (80.6%) patients. The most common cause / risk factor of CTS in this sample was obesity (66; 37.7%).

Conclusion: The demographic pattern and clinical features of this sample of CTS patients in Kuwait are similar to what was found elsewhere.

KEYWORDS: demographics, entrapment neuropathy, median nerve, signs and symptoms

INTRODUCTION

Carpal tunnel syndrome (CTS) is a neurological disorder of the median nerve characterized by sensory symptoms of the first three fingers and radial half of the fourth finger[1-2]. It is considered as the most common upper limb compression neuropathy accounting for approximately 90% of all entrapment neuropathies[3-5]. In Sweden, the prevalence of CTS in the general population was estimated to be 3.8%, with one out of five subjects with hand symptoms of pain, numbness and tingling would be expected to have this disorder[6]. Also, a prospective population-based study conducted in Netherlands in 1985 among 715 participants aged 25 to 74 years revealed that the prevalence of CTS was 6.6% in men and 5.8% in women[7]. One more study done in the general practice setting using data from Dutch National Survey to study the incidence of CTS in 1987 and 2001 showed that the crude incidence rate was 1.3 per 1000 in 1987, and 1.8 per 1000 in 2001[8]. The incidence rate was higher among females (female:male ratio was 3:1:1) during both years of their study, and its peak was among the 45 - 64 years age group. Moreover, the overall incidence of this condition in Minnesota, United States of America (USA), was 376 per 100,000 person-years in 1981-2005[9]. In western Saudi Arabia, a retrospective study involving 135 patients without
any predisposing condition to CTS, and diagnosed as CTS using electrophysiological studies revealed that the male:female ratio was 1:4.9 and the condition was commonest among the age group 45 - 54 years[10]. The economic costs of medical and surgical treatment of CTS were very high in the USA[11-12]. An estimated one million cases require medical treatment for CTS, while more than 400,000 cases require surgical treatment. This huge number of operations costs more than $2 billion per year. In the United Kingdom (UK), the surgical operation rates for CTS are 43 to 74 operations per 100,000 per year[13].

CTS is caused by various occupational and non-occupational causes[14]. Repetition, force, posture, external pressure and vibration are physical factors that were demonstrated to cause CTS. On the other hand, the non-occupational causes can be categorized into local, regional and systemic. The local causes include inflammation (e.g., tenosynovitis and infections), trauma (e.g., Colle’s fracture and dislocation of the carpal bones), tumors (e.g., hemangiomas and ganglion), and anatomical anomalies (e.g., thickened transverse carpal ligament and bony abnormalities). Osteoarthritis, rheumatoid arthritis, amyloidosis and gout are considered regional causes of CTS, while diabetes, obesity, hypothyroidism, pregnancy, menopause, systemic lupus erythematosus, scleroderma and acromegaly, among other conditions, are considered systemic causes.

Patients with CTS may present with tingling, numbness, burning sensation and pain over the distribution of the median nerve that typically increase during sleep, and resolve by shaking and moving the wrist[15]. On physical examination, sensory deficits (e.g., diminished pinprick sensation), and thenar muscle atrophy and weakness might be noted[16]. Moreover, Phalen’s test (flexion of the wrist for 30 - 60 seconds to induce or increase the symptoms) and Tinel sign (tapping over the site of the median nerve to induce tingling) are commonly used to aid in the diagnosis of CTS[16-18]. Other physical examination signs, such as carpal tunnel compression test and hand elevation test, can also be used. Furthermore, adding data from nerve conduction studies (NCS), electromyogram (EMG) and ultrasonography (US) confirm the diagnosis of CTS[19-21].

The treatment of CTS can be non-surgical or surgical depending on the severity of the disease and the patient’s preference[14,22]. Splinting, rehabilitation modalities (stretching and strengthening, and therapeutic ultrasound), oral medication (e.g., corticosteroids, vitamin B6 vitamin B12, and non-steroidal anti-inflammatory drugs) and local injection of corticosteroids are options for conservative management. On the other hand, the surgical treatment of CTS can be either open or endoscopic carpal tunnel release.

In Kuwait, it was reported that the prevalence of CTS among office workers is 18.7%; however, no studies described the demographic pattern and clinical features of this syndrome in Kuwait[23]. By conducting this study, we aimed to provide a description of the demographic pattern and clinical features of patients with CTS presenting to orthopedic outpatient clinics of Jaber Al-Ahmad armed forces hospital in Kuwait.

SUBJECTS AND METHODS

We retrospectively reviewed the medical records of Kuwaiti patients who presented to our orthopedic outpatient clinics and were diagnosed with CTS from January 2006 to December 2010. Our hospital is the only military hospital responsible for the care of employees of the Ministry of Defense and their relatives in Kuwait. Patients with suspected CTS presenting to doctors from other departments in our hospital are transferred to orthopaedic surgeons for diagnosis and treatment; however, it is the patient’s choice to continue treatment in this hospital or to be transferred to other hospitals belong to the Ministry of Health in Kuwait (Neurosurgery and Orthopedic hospitals). The diagnosis of CTS was based on a combination of findings from the patient’s history (sensory symptoms of the hands and digits such as numbness, tingling, pain and nocturnal parasthesia) and physical examination (signs of median nerve disease such as thenar muscle bulk and strength, abnormal sensation over the median nerve distribution, Phalen’s test and Tinel sign) that was further confirmed by EMG and NCS of the median nerve[24]. Files with incomplete information were excluded. The study protocol was reviewed and ethically approved by our institutional projects’ review committee.

One hundred and seventy-five patients were included in the study. Nineteen patients were excluded from the study because of missing data in their files. We gathered the demographic data along with the clinical features of CTS for each patient. This included age, gender, symptoms, physical examination findings and the site of CTS. We also collected data about possible causes or risk factors of CTS in our patients. These data were analyzed using the Statistical Package for Social Sciences (SPSS), and were presented using frequencies and percentages.

RESULTS

Table 1 demonstrates the demographic pattern and clinical features of CTS in our cohort of patients. The age of our sample ranged from 25 to 70 years (mean ± standard deviation = 43.68 ± 8.737), with a peak age of 46 - 50 years (40; 22.9%). Out of the 175 patients,
114 (65.2%) developed CTS between the age of 36 to 50 years. Forty-three (24.6%) patients were male and 132 (75.4%) were female, with a male to female ratio of 1:3.1.

Symptoms were present in 172 (98.3%) patients during the daytime, while nocturnal symptoms were present in all patients (Table 1). Physical examination revealed abnormal sensation in 150 (85.7%) patients and a positive Phalen’s test in 161 (92.0%). Tinel sign was present in 129 (73.7%) patients. Moreover, wasting (17; 9.7%) and decreased power (91; 52.0%) of the thenar muscle was found in some patients. Bilateral CTS was diagnosed in 141 (80.6%) patients, and unilaterally in 34 (19.4%). In unilateral cases, right side (24; 13.7%) was involved more than the left side (10; 5.7%).

Factors known to be associated with increased risk of CTS in our patients are shown in Table 2. The most common associated factors of CTS in this sample were obesity (66; 37.7%) and diabetes (49; 28.0%). On the other hand, recurrence of CTS after surgical treatment, gout, osteoarthritis and acromegaly were the least common associated factors (1; 0.6%). No associated factor for CTS (idiopathic) was found in 43 (24.6%) patients.

**DISCUSSION**

This is the first study of the demographic pattern and clinical features of CTS patients in Kuwait; however, it is limited by the small number of patients which may result in data that are not representative of the whole population of Kuwaiti CTS patients. As expected, excess of females over males was noted; however, the male to female ratio (1.3:1) was more than UK (1:2.07) and USA (1:2.2) but less than Eastern province of Saudi Arabia (1:4.6), Argentina (1:10) and Korea (1:23) [9, 10, 25-26]. Moreover, the age of diagnosis (middle-age) and the site of involvement (most commonly bilateral, and right hand more than left hand) were similar to what was reported elsewhere [9, 14-15, 22, 23]. The common bilateral involvement of CTS in our sample is most probably due to the high prevalence of diabetes mellitus and obesity among these patients [27-28]. In Saudi Arabia, bilateral CTS were found to be more common than unilateral because obesity and diabetes mellitus were highly prevalent in their population (84% and 30% respectively) [20]. The minor differences noted in the demographic data are probably due to the different modalities used to diagnose CTS among different researchers and the sample size of each study.

Regarding symptoms of CTS in our patients, only 1.7% did not complain of daytime symptoms,
while all patients had nocturnal complaints. This is similar to what was reported by Kendall, where few patients reported symptoms only during the day[30]. Also, similar to Kendall’s patients, almost all (85.7%) patients in our study had abnormal sensation during physical examination. The results of Phalen’s test (positive in 92.0%) and Tinel sign (present in 73.7%) among our patients reflect the higher sensitivity of the test[16-18]. In addition, motor examination abnormalities, which are thenar muscle wasting (9.7%) and weakness (52.0%), were reported less than sensory abnormalities because motor symptoms and signs are known to be late manifestations of CTS[19].

The literature suggests that in only 50% of patients a possible cause / associated factor for CTS is not found[14]. A possible cause / associated factor of CTS in our study was not identified in about one quarter of patients; however, these patients did not have imaging examination (e.g., US and magnetic resonance imaging) of the wrist which can identify a cause of CTS in some cases[31]. Obesity and diabetes were present in more than 25% patients. Increasing cases of CTS resulting from obesity and diabetes is expected in Kuwait and other countries in the middle-east and western countries where obesity and diabetes are highly prevalent.

CONCLUSION

In conclusion, this sample of CTS patients in Kuwait share similar demographic pattern and clinical features to CTS patients elsewhere with minor differences in male to female ratio. The syndrome was more common in females and middle-aged individuals. The majority of cases had bilateral disease, most probably because of the high prevalence of systemic diseases, such as diabetes mellitus and obesity, among our population. Sensory symptoms and signs were more common than the motor ones. The most common causes / risk factors of CTS in Kuwait were obesity and diabetes.

REFERENCES


Case Report

Squamous Cell Carcinoma of the Gall Bladder Masquerading as a Liver Abscess

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ABSTRACT

The most common gall bladder malignancy is an adenocarcinoma. Other types of malignancies are rarely reported in the gall bladder (GB). We report a rare case of squamous cell carcinoma of the GB in a 35-year-old Bangladeshi lady who presented with signs and symptoms of a big liver abscess and normal tumor marker (CA-19.9) levels.

KEY WORDS: cancer, gall bladder, liver abscess, squamous cell carcinoma

INTRODUCTION

Gall bladder (GB) cancer is the fifth most common malignancy of the gastrointestinal tract¹,². It is usually discovered incidentally after a cholecystectomy for calcular biliary disease. Adenocarcinoma is the most common malignant gall bladder tumor. Squamous cell carcinoma (SCC), papillary, anaplastic and angiosarcomas are rare GB malignancies. Most reports of a SCC of the GB are found to be mixed with another type of gall bladder malignancy. The reported incidence of pure SCC accounts for almost 1.4 - 3.3% of all GB cancers¹,³.

CASE REPORT

A 35-year-old Bengali female, with diabetes mellitus, was admitted to the medical ward as a case of severe non-biliary pancreatitis complicated with bilateral pleural effusion. Abdominal ultrasound (US) and CT scans showed a hypodense GB bed lesion with mildly enhanced margins (Fig. 1a, b, c). Unfortunately, after her pancreatitis improved, she was discharged from hospital by her employer before the gallbladder lesion was thoroughly evaluated.

A year later, she presented to the surgical ward with pain in the upper abdomen, associated with nausea, vomiting and high fever. On examination, she looked ill and febrile with tachycardia. There was tenderness in the right hypochondrium and epigastrium with guarding and a big tender mass arising from the liver with severe tenderness on the lower intercostals. Her liver function tests showed only a high alkaline phosphatase (239 IU/l) and normal serum bilirubin. She was provisionally diagnosed as a possible case of liver abscess versus liver tumor with central necrosis.

Serology screening for amebiasis and hydatid cyst were negative. Tumor markers (AFP, CA-19.9, CEA and CA-125) were negative. ERCP showed normal extrahepatic ducts with extravasation of the contrast from the gall bladder into a big irregular cavity in the liver (Fig. 2a). Percutaneous transhepatic aspiration under fluoroscopy from the cavity revealed thin turbid fluid which was sent for cytology. It was reported later as non-conclusive.

A CT scan showed a large 11.5 x 7.7 x 11.4 cm lobulated inhomogeneous hypodense lesion occupying segments IV, V & VI of the liver (Fig. 2b). It showed post-contrast peripheral incomplete enhancement of the lesion with non-enhancement of a central big cavity consistent with features of an abscess cavity within the liver (segments IV, V &VI). A Gallium study showed photopenic lesion within the right liver lobe that was consistent with the radiological finding of necrotic liver tissue or liver abscess.

The patient continued to be septic despite potent intravenous antibiotic therapy. Surgical exploration was decided which revealed a big GB tumor infiltrating the liver and abdominal wall with many seedlings all over the liver. The case was considered inoperable and

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a biopsy was taken for histopathology which showed a SCC of the GB. She was managed symptomatically with analgesics and intravenous antibiotics but she continued to be septic and was deteriorating with time. She passed away two weeks after the final diagnosis was reached.

DISCUSSION

Pure SCC of the gallbladder accounts for almost 1.4 - 3.3% of GB cancers[1-3]. It is mostly found mixed with other types of metaplasia of the GB and these account for almost 12% of the GB carcinomas[4,5]. SCC of the GB is more common in females with a F:M ratio of 3:1. It presents at an earlier age (4th - 6th decade) than adenocarcinoma. It grows rapidly, metastasizes early and has a worse prognosis. It has a direct local and regional spread with rare lymph node and peritoneal metastasis[1,6-8].

In the case presented here, the patient was in the middle of her 3rd decade. In consistence with what is known about the pattern of spread of SCC of GB, there was direct local spread involving the liver at the time of diagnosis with severe necrosis giving the impression of a liver abscess or a GB empyema perforating into the liver.

Different hypotheses were put forward for the development of SCC in the GB: i) malignant transformation of heterotopic squamous epithelium ii) malignant transformation of metaplastic squamous epithelium or iii) squamous metaplasia of adenocarcinoma[1,6]. In the case reported here it seems that malignant transformation of squamous epithelium is more likely since the histopathology examination did not observe the presence of any adenocarcinomas or any cell in the transitional stage between adenocarcinoma and SCC.
In SCC, the extent of the tumor at the time of diagnosis is the most important indicator for survival. The average reported survival rate is about six months after diagnosis when radical surgery was not possible. Perhaps because SCC is a rare tumor, there are no published data that show improvement of survival or the quality of life after radiotherapy or chemotherapy in these patients.

Unfortunately during the first admission this patient was prematurely discharged from hospital. During the second admission, though malignancy was thought of but the severe sepsis, the leak of contrast from the GB into the liver on ERCP, the aspiration of turbid thin fluid from the lesion and the negative tumor markers confused the issue.

CONCLUSION

SCC of the gall bladder is a rare, aggressive lesion which presented to us late with sepsis and features consistent with a liver abscess.

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Case Report

A Rare Case of Appendiceal Stump Adenocarcinoma and Review of Literature

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ABSTRACT

Adenocarcinoma of appendiceal stump is extremely rare, with only four such patients reported to date. It has no specific clinical signs, symptoms, or radiologic features, making preoperative diagnosis difficult. Secondary right hemicolectomy is recommended and is difficult to perform, with peritoneal dissemination and lymph node metastases sometimes found at the second operation. We report on a case of a 72-year-old patient who underwent an appendectomy in 2005 and was admitted because of a 3-month history of repeated constipation with vomiting. He was not relieved with the use of gastrokinetic drugs. Initial diagnosis was chronic adhesive intestinal obstruction due to previous lower abdominal surgery. He recovered well postoperatively. A histological examination showed a well-differentiated adenocarcinoma of the appendiceal stump.

KEY WORDS: adenocarcinoma, appendectomy, appendiceal stump

INTRODUCTION

Since appendectomy is usually performed for patients with appendicitis, patients with an appendiceal stump are not uncommon. Malignant tumors of the appendix, however, are rare and adenocarcinoma involving the post-appendectomy appendiceal stump is extremely rare, with only four such patients reported to date\[^{[2]}\]. This diagnosis cannot be determined until laparotomy or pathologic evaluation of the appendectomy specimen. Reoperation, consisting of right hemicolectomy, is recommended in patients diagnosed with adenocarcinoma of the appendiceal stump after pathologic evaluation of an appendectomy specimen\[^{[2]}\].

CASE REPORT

In September 2010, a 72-year-old man was admitted to our institution with a 3-month history of repeated constipation along with vomiting. He had undergone an appendectomy in 2005 due to acute appendicitis. Since then, he had remained well. The pathological results of the lesion and the sections were not available. On admission, no obvious abnormality was found, except for a decrease in bowel sounds. There was no family history of cancer or colon polyps.

His hemoglobin concentration was 105 g/l (normal, 110 - 165 g/l), his white blood cell count was 9.5 x 10\(^9\) cells/l (normal, 3.5 - 10.0 x 10\(^9\) cells/l), and neutrophil were 77.10\% (normal, 50 - 70\%). Biochemical analyses were within normal range. During the last three months, he was managed conservatively, including fasting with fluid support and tube decompression when intermittently admitted to a local hospital on three occasions. Since his symptoms were partially alleviated by administration of gastrokinetic drugs with no obvious positive findings on abdominal X-ray, he was initially diagnosed as a case of intermittent incomplete adhesive intestinal obstruction due to lower abdominal surgery. As the diagnosis remained obscure, we carried out an endoscopy examination for the old man to rule out malignancy. Colonoscopy only showed an obscure view of the ileocecal valve opening and inflammatory changes in the mucous membrane of the colon.

During this hospitalization, he experienced abdominal discomfort. At the urging of the patient and his family, an exploratory laparotomy was performed six days after admission due to unalleviated abdominal pain. At exploratory laparotomy, we observed no obvious adhesions in the abdominal cavity. We also

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found thickening of 50 cm of the terminal ileum, indicative of chronic obstructive changes, as well as inversion of the preileal appendiceal stump around the ileocecal valve. The stump mass had a diameter of 2.5 - 3.0 cm and felt somewhat hard. The stump mass was resected because of its potential for incomplete constriction of the ileocecal valve, leading to obstruction. Although he recovered well, histological examination of the resected mass showed that it was a well-differentiated adenocarcinoma of the appendiceal stump (Fig.1). The patient refused to undergo a right hemicolectomy, and he was discharged 10 days after the exploratory laparotomy.

DISCUSSION

Malignant tumours of the appendix are rare, with the rarest type being adenocarcinoma arising from the appendiceal mucosa. Appendiceal malignancies have no specific clinical signs, symptoms, or radiologic features, making preoperative diagnosis difficult. Adenocarcinoma of the appendix has been found in only 0.080% of appendices removed for disease, incidentally or at autopsy[1-3].

The two specific criteria of carcinoma of the appendix are: 1) continuity of the carcinoma with the appendiceal mucosa; and 2) presence of neoplastic acini containing mucin, thus excluding simple mucocele of the appendix[4]. Since the muscular layers of the appendix are frequently incomplete or absent, direct extension to adjacent structures may occur early[5].

An extremely rare subcategory of adenocarcinoma of the appendix is adenocarcinoma involving the post-appendectomy appendiceal stump. The first such case was described in 1903; at autopsy, a carcinoma was found in the stump of an appendix that had been removed six years previously[6]. Since then, only four definitive instances of appendiceal stump carcinoma have been reported[1,3,6-7], including a 54-year-old male with a mucocele of the appendiceal stump 25 years after appendectomy. That tumor was 20 cm in diameter and filled with mucus, which produced a mucocele.

There is no clear evidence of a correlation between removal of the appendix and subsequent development of adenocarcinoma in the appendiceal stump. Radiographically, an inverted appendiceal stump appears as a round, smooth filling defect in the cecal tip at the expected location of the appendix. Some inverted stumps may not be smooth and may have some irregularities, including sharp margins, most likely related to suture granuloma, but the appearance of these stumps may be similar to that of a true neoplastic polyloid lesion.

Radiologic differential diagnosis in post-appendectomy patients with such a finding includes an unusual inverted appendiceal stump, adenomatous polyp, carcinoid of the stump, inflammatory changes, and carcinoma of the cecum or appendiceal stump. Thus, unless previous films are available to document the lack of change in size and configuration, irregular filling defects in the cecal tip must be evaluated by colonoscopy to rule out neoplasm.

Inverted appendiceal stumps may be misdiagnosed as a polyp, granuloma, or lipoma of the cecum. The appendiceal stump can also occasionally cause hemorrhage or ileocolic intussusception. Appendiceal carcinoma is rarely correctly diagnosed preoperatively, with the most common preoperative diagnosis being appendicitis. The rarity of appendiceal carcinoma and its similar presentation to appendicitis make a correct diagnosis difficult.

Among the diagnostic tools available to avoid reoperation are assays for cancer biomarkers in blood. Endoscopically detectable blockage of the ileocecal valve opening is not diagnostic for neoplasms because it may prevent expulsion and cause appendicitis. Endoscopic ultrasonography (EUS) may be useful as also a frozen section examination.

Adenocarcinoma of the appendix may be treated by right hemicolectomy with lymph node dissection, rather than appendectomy. Secondary right hemicolectomy has been recommended, with the risk of recurrence dependent on the degree of histological differentiation and the stage at diagnosis. Thus, surgical method should be determined case by case. In practice, secondary right hemicolectomy following an appendectomy is difficult to perform, with peritoneal dissemination and lymph node metastases sometimes
found at the second operation. Frequently, the only diagnosis possible, even at operation, is an ileocecal mass, for which an ileocecal resection should be performed[1, 2, 4, 7].

CONCLUSION
Although appendiceal stump adenocarcinoma is rare, surgeons should be aware of possibility of malignancies arising from the stump. Furthermore, they should carefully try to review pathology results of the appendix specimen if available and evaluate patients with chronic obstruction, right lower quadrant pain by CT scan with contrast and colonoscopy. These are the best type of investigation for post-appendectomy abdominal pain. Also, patients should be informed about risks of potential secondary right hemicolecction.

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Case Report

Squamous Cell Papilloma of the Stomach

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ABSTRACT

Benign tumors in the stomach are rare in comparison with malignant tumors. Squamous cell papilloma (SCP) of the stomach is a relatively rare benign tumor and only few case reports are found in the literature. Herein, we report a case of squamous cell papilloma of the gastric cardia and also a review the relevant literature.

KEY WORDS: adenocarcinoma, gastric cardia, gastrectomy, ulcerative mass

INTRODUCTION

The incidence of gastric tumors varies, depending on geographical location and ethnic background [1]. Generally speaking, gastric adenocarcinoma is relatively common and comprises over 90% of all gastric tumors in the world, especially in many Asian countries. This suggests that the environmental and dietary factors are probably responsible [2]. On the contrary, the occurrence of benign tumor (1.3 to 2.0 percent) in the stomach is rare in comparison with gastric cancer [3]. Even more, in some articles, squamous cell papilloma (SCP) was usually noted in gastrointestinal system except the stomach and hard to distinguish from malignant tumor of the stomach [4]. Morphologically, the development of benign tumors is characterized by a two stage model, including early lesions such as epithelial damage, hyperplasia and hyperkeratosis, and later stage such as diffuse hyperplasia, dysplasia, papilloma and squamous-cell carcinoma [5]. On reviewing previous literature, very rare case reports about squamous cell papilloma (SCP) of the stomach were found [6,8-11]. SCP of the stomach is a comparatively rare lesion and there is scant literature on this subject. It was even noted on necropsy findings [6,9]. Because of the reasons mentioned above and the fact that a benign tumor may take on malignant characteristics [7,8], we report a case of primary SCP of the gastric cardia.

CASE REPORT

A 29-year-old fireman presented with progressive swallowing difficulty and pain in the epigastric area for three months. The symptoms were exacerbated by eating solid food. A body weight loss of 5 kg was also noted. Physical examination showed only mild tenderness in the epigastric area. Esophago-gastro-duodenoscopy revealed an erosive and ulcerative mass in the gastric cardia (Fig. 1). Chest and abdominal computed tomography (CT) showed a heterogeneous density mass at the gastric cardia (Fig. 2). Total gastrectomy was performed because of a high suspicion of malignancy. On gross examination, there was an ill-defined polypoid lesion, measuring 5.5 x 4.4 x 2.1 cm in the gastric cardiac region. Microscopically, papillary squamous epithelium with parakeratosis and hyperkeratosis was noted (Fig. 3).

DISCUSSION

Customarily, benign gastric tumors were classified according to their histogenetic origin. Adenoma and leiomyoma preponderantly comprise more than 90% of all benign tumors of the stomach [12]. However, SCP of the stomach was scarcely seen in published articles [4,10,12]. Only rare case reports about SCP of the stomach were found [2,6,8,9,11].

SCP of the stomach may be located at antrum, pylorus and greater or lesser curvature [2,8,9]. To date, only one article regarding SCP at the gastric cardia was found [13].

Ectopic squamous epithelium appears to be extremely rare in the stomach [14], but squamous metaplasia has been described in some articles [15].

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Though the real pathogenesis of SCP of the stomach remains unknown, two theories including squamous metaplasia of the gastric mucosa before malignant existing adenocarcinoma were proposed.

CONCLUSION

SCP of the gastric cardia is quite rare. This particular case report emphasizes consideration of this condition as a differential diagnosis in gastric tumors.

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Case Report

Triple Synchronous Primary Cancers of Thyroid, Bladder and Prostate: A Case Report

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ABSTRACT

Multiple primary cancer is defined as two or more cancers in a single patient. Although the presence of bladder and prostate carcinoma in the same patient is not a rare event, third primary malignancy in patients with bladder and prostate carcinoma is rare. In this report, we present a patient who developed synchronous multiple primary cancers including bladder, prostate and thyroid papillary cancer within a five-month period. This combination of synchronous multiple primary carcinomas, according to the best our knowledge, has never been reported in the literature.

In conclusion, the possibility that multiple primary malignancies exist must always be considered during pretreatment evaluation. The focal thyroid ²⁻¹¹I uptake values warrants a pathological diagnostic procedure.

KEY WORDS: prostate, synchronous multiple primary neoplasms, thyroid gland, urinary bladder

INTRODUCTION

Multiple primary cancer (MPC) is defined as two or more cancers in a single patient. Each tumor is independent rather than a metastasis from another tumor and it does not have any relationship with each other. Moertel et al classified MPC observed at the same time or within six months as synchronous MPC, and cancers developing with more than six months as an interval as metachronous multiple primary cancers[1].

A previous study defined the incidence of MPC, which also included autopsy cases, as 1.8 - 11% of all cancers[2]. The presence of bladder and prostate carcinomas in the same patient is not a rare event. Chun reported that the rate of bladder carcinoma in patients with prostate carcinoma is eighteen times higher[3]. However, a third primary malignancy in patients with bladder and prostate carcinoma is rare. In this report, we present a patient who developed synchronous MPC including bladder, prostate and thyroid papillary cancer within a five-month period. This combination of synchronous MPC, according to our knowledge, has never been reported in the literature.

CASE REPORT

A 62-year-old male presented with hematuria and frequent urination in August 2010 from another hospital. The patient underwent transurethral resection of the bladder tumor (TURB) and histopathology revealed it to be a transitional cell carcinoma with lymph node metastasis, prostate and muscle invasion. The vital signs and physical examination were normal. Routine hematolog and blood biochemistry investigations were normal. Serum freeT3 was 3.82 ng/dl (normal range 1.80 - 4.60 ng/dl), freeT4 1.18 ng/dl (normal range 0.93 - 1.70 ng/dl) and thyroid stimulating hormone 2.20 μIU/ml (normal range 0.27 - 4.20 μIU/ml). Hematuria and pyuria was found in urine analysis. He had no previous history of malignancy, chemotherapy or radiotherapy and there was no family history of malignancy. The patient underwent radical cystectomy and urinary diversion.

The pathology report showed invasive urothelial carcinoma and prostate adenocarcinoma. There was invasion of the muscle tissue, 8 of 14 lymph nodes, vesicular seminalis and prostate. Gleason

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score of prostate was six. The tumor was staged as grade 4 (T4aN1Mx) and the patient was started on chemotherapy including gemcitabine plus cisplatin combination. Computerized tomography scan of the abdomen prior to cystectomy was unremarkable except for cystic lesions in the liver. Postoperative prostate specific antigen (PSA) value was 0.01 ng/ml (normal range 0.0 - 5.4 ng/ml).

A 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) performed two months later revealed thyroid uptake, with a maximum standardized uptake values (SUVmax) of 46. Thyroid ultrasonography revealed a 1.5 cm solid nodule in the right thyroid lobe. Fine needle aspiration (FNA) of this nodule was done and the biopsy specimen was stained with Papanicalau (PAP) stain. On microscopic evaluation, the specimen was hypercellular and composed of true papillary structures lined by tumor cells having large eosinophilic cytoplasm, intranuclear pseudo inclusions and nuclear grooves. According to these findings our diagnosis was consistent with “papillary thyroid carcinoma” (Fig. 1). Afterwards total thyroidectomy and mediastinal lymph-node dissection was performed. Macroscopic examination of thyroid gland showed yellowish white, solitary, 1.5 x 1 x 1 cm sized nodular lesion in the right lobe. Histopathologic examination of this nodule revealed a well-circumscribed, colloid poor tumoral lesion. The tumor consisted of follicular papillary structures containing large eosinophilic cytoplasm, intranuclear pseudoinclusions and nuclear grooves. The diagnosis again was “papillary thyroid carcinoma” (Fig. 2). He was treated with radioactive iodine (I-131) and started on L-thyroxin.

The patient was given fourth time chemotherapy including gemcitabine plus cisplatin combination for bladder cancer. FDG-PET/CT was normal after chemotherapy for the fourth time.

**DISCUSSION**

Among those with multiple primary malignancies, double cancer is commonly seen, while triple or quadruple or quintuple cancers occur in less than 0.1% of the population. Improved diagnostic techniques and increased elderly patient populations have also been indicated as possible causes. Although the mechanism for the pathogenesis of MPC has yet to be clarified, some factors such as heredity, constitution, and environment, and immunology and carcinogens (viruses, radiotherapy and chemical treatments) have been implicated.

MPC could develop in the same system (e.g., in the genitourinary system). The presence of bladder and prostate carcinomas in the same patient is not rare event. Chun reported that the rate of bladder carcinoma in patients with prostate carcinoma is 18 times higher and the rate of prostate carcinoma in those with bladder carcinoma is 19 times higher than expected. Although bladder and prostate carcinoma can co-exist in the same individual frequently enough, the rare event is the appearance of a third malignancy.

FDG-PET / CT imaging has been used extensively in the diagnostic work-up and the follow-up of a variety of cancers in medicine and oncology clinics. However, several studies have demonstrated, like the present case, the incidental detection of synchronous malignancies by performing PET. Thyroid FDG-PET / CT incidentaloma has prevalence of 2.2%. The focal thyroid FDG-PET / CT incidentaloma carries a high risk of malignancy, especially in cases with high SUVs as was the case in our patient.

Papillary thyroid cancer is most frequently sporadic but can also be familial or associated to other cancers, mainly colorectal cancer, as well as
to other autosomal dominant pathologies (familial adenomatous polyposis, Gardner syndrome, Cowden syndrome, Werner syndrome, Carney complex, Peutz-Jeghers syndrome etc.). Among patients with papillary thyroid cancers, malignant lesions were found in other sites (such as breast, larynx, basal cell carcinoma, colon and rectum, uterine cervix, endometrium, ovary, renal, lung) in 3.5 - 20%. The most frequent sites were colon and rectum, representing 15% of all associations. Both diagnoses were simultaneously found in 8% of cases while the extra-thyroidal malignant tumour was found after the papillary thyroid cancer in 12%[7,8].

A case of synchronous multiple primary malignancy including rectum, uterine cervix and thyroid was reported by Lee JS et al[9]. Another case of MPC including squamous cell carcinoma of the lung, transitional cell carcinoma of the renal pelvis and bladder, prostatic carcinoma and thyroid carcinoma was reported by Kobayashi K et al[10]. To the best of our knowledge, although there are a few report about this combination of MPC[10], synchronous bladder, prostate and thyroid papillary cancer has never been reported in the literature. In this report, we present a patient who developed synchronous MPC including bladder, prostate and thyroid papillary cancer.

CONCLUSION

In conclusion, the possibility that multiple primary malignancies co-exist must always be considered during pretreatment evaluation. The focal thyroid FDG-PET / CT incidentaloma with high SUVs warrants a pathological diagnostic procedure.

REFERENCES

Case Report

Successful In Situ Reconstruction with a Prosthetic Graft in Tuberculous Pseudoaneurysm of Abdominal Aorta: Two Case Reports

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ABSTRACT

Tuberculous pseudoaneurysm (TP) of the abdominal aorta is an exceedingly rare and life-threatening disease. Here, we report two patients treated with a combination of in situ reconstruction with a prosthetic graft and antitubercular therapy. The first case was a 51-year-old man with an infrarenal abdominal aortic pseudoaneurysm; the second case was a 56-year-old man with an infrarenal abdominal aortic pseudoaneurysm and a paraspinal abscess at three months after endovascular stent-graft repair for abdominal aortic dissection. Both patients had a history of tuberculosis (TB) and presented with lumbar or abdominal pain. The extensive debridement of infected tissues and in situ reconstruction with a prosthetic graft were performed with laparotomy. Pathological examination of the periaortic and aortic wall revealed chronic inflammation with TB infection. Therefore, in situ reconstruction with a prosthetic graft and antitubercular therapy offer favorable results in TP of the abdominal aorta.

KEYWORDS: aorta abdominal, blood vessel prosthesis, pseudoaneurysm, tuberculosis

INTRODUCTION

Tubercular involvement of aortic wall is a rare phenomenon. With worldwide resurgence of tuberculosis due to an increasing incidence of drug-resistant tuberculosis and its association with acquired immunocompromised condition1,2. The incidence of tuberculous pseudoaneurysm (TP) has arisen as a significant clinical entity3. Symptomatic TP becomes a fatal lesion, if not diagnosed and treated promptly. This report describes two cases of successful in situ reconstruction with a prosthetic graft of TP of the infrarenal aorta secondary to TB. The pathogenesis, clinical features and management of TP are also reviewed.

CASE REPORT

Patient 1

A 51-year-old man presented with constant lower gastric pain radiated to the right shoulder and back lasting for one month. He did not complain of nausea, vomiting, diarrhea, or fever. He was diagnosed as a case of pulmonary TB seven months ago and received antitubercular therapy. A purulent lump was found in his left epididymis and it was surgically removed two week ago. Physical examination revealed a pulsatile mass located at the right quadrant of the abdomen reaching the level of navel with an obscure boundary, limited degree of excursion, and non-tender to palpation. Enhanced computerized tomography (CT) scan demonstrated dilatation of the abdominal aortic lumen and chronic inflammatory infiltration of the vessel wall (Fig. 1a). CT angiography exhibited a saccular pseudoaneurysm measuring 8 x 6 cm in the infrarenal abdominal aorta without involving bilateral renal artery and bilateral iliac artery (Fig. 1b). An obvious laceration was observed at the lateral wall of the infrarenal abdominal aorta. The patient was diagnosed as a case of TP of the infrarenal abdominal aorta due to the history of TB and typical finding of CT scan.

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The symptom of persistent pain was believed to be the sign of impending rupture. A laparotomy was performed which confirmed the existence of a TP arising from the lateral wall of the infrarenal abdominal aorta. Once aneurysmal wall was opened, massive cheesy necrotic tissue and light coffee-colored purulent liquid poured out of the aneurysmal sac. Lymphatic vessels were found to be markedly dilated in the aortic wall, and chyle flowed out of dilated vessels intraoperatively. The observed red and white thrombi were attached to the intimal surface of the involved aortic wall. The maximal diameter of expanded aorta was approximately 3 cm, and the aortic wall around the vantage was hardened and brittle. After extensive debridment of the periaortic necrotic tissue and removal of the diseased segment of aorta, the operating field was washed repeatedly with 1.0 g of streptomycin and 0.2 g of Armazide diluted in 500 ml of saline. With macroscopically disease-free margin, in situ aortic reconstruction was performed by means of a prosthetic graft. The pedicle wall flap was used to cover the anastomosis site. Drainage tubes were inserted into the lower abdominal incision sites. The pathological examination (performed by the Department of Pathology, Shanghai Hospital, Second Military Medical University, Shanghai, China) of the periaortic tissue and aortic wall revealed a combination of acute and chronic inflammation with multinucleated giant cell reaction. The patient received antitubercular drugs with isoniazid, rifampicin, and ethambutol on the first day following the operation. The patient’s postoperative course was uneventful, and he was discharged at week two after admission. At the 6-month follow-up, the patient remained well and asymptomatic; CT angiography revealed that the periangiitis around the abdominal aorta completely

Fig. 1: Tuberculous false aneurysm of infrarenal abdominal aorta in a 51-year-old male. (a) Enhanced CT scan demonstrating the dilatation of abdominal aorta and inflammatory thickening of the vessel wall. (b) CT angiography showed a saccular false aneurysm measuring 8 x 6 cm in the infrarenal abdominal aorta without involving bilateral renal artery and bilateral iliac artery. (c) Postoperative CT scan exhibited smooth abdominal aortic wall and complete disappearance of periangiitis. (d) Postoperative CT angiography showed the normal profile of abdominal aorta.
disappeared and the vessel wall became smooth (Fig. 1c). A normal profile of abdominal aorta was simultaneously observed on enhanced CT scan (Fig. 1d).

Patient 2

A 56-year-old man presented with an abdominal mass persisting for 10 days at three months after endovascular stent-graft repair for pseudoaneurysm of the abdominal aortic dissection. He had been complaining of waist and back pain and intermittent fever since the stent-graft implantation. However, a pulsatile mass was detected in the right lower quadrant of the abdomen at ten days before admission, and was associated with persistent gastric pain in this region. Six days prior to admission, the mass increased markedly in size and the pain worsened. The patient developed sweating all over his body, his face turned pale, and his blood pressure dropped significantly at the same time. CT scan at the local hospital showed a large saccular mass in the right lower quadrant. A CT scan done two days later revealed that the mass had dilated significantly. The patient received an emergency transfer to our hospital due to a suspected impending rupture of the aneurysm. On admission, the patient's vital signs were stable (blood pressure: 105 / 76 mmHg, pulse rate: 106 beats/min, respiration rate: 24 breaths/min, body temperature: 36.4 °C). Physical examination revealed an increased tactile fremitus and a dull percussion sound in the right lower lung. The rest of physical examination revealed a pulsatile mass extending to the right waist and back with clear

Fig. 2: Tuberculous false aneurysm of infrarenal abdominal aorta after endovascular repair for abdominal aortic dissection in a 56-year-old male. (a) The enhanced CT scan showed a huge heterogeneous enhanced mass about 25 x 20 cm in size in the right lower quadrant. (b) Magnetic resonance imaging showed a neighboring paraspinal abscess. (c) CT angiography showing a saccular false aneurysm of the infrarenal aorta without involving the bilateral iliac arteries. (d) Postoperative CT angiography demonstrated the continuity of the abdominal aorta.
boundary and tenderness; nevertheless, no vascular murmur was heard. Enhanced CT scan demonstrated a huge heterogeneous enhanced mass about 25 x 20 cm in size in the right lower quadrant (Fig. 2a). Magnetic resonance imaging demonstrated erosion of the anterior aspect of the fourth lumbar vertebral body on the left side with a neighboring paraspinal abscess (Fig. 2b). CT angiography demonstrated a saccular pseudoaneurysm of the infrarenal aorta without involvement of the bilateral iliac arteries (Fig. 2c).

The patient underwent an emergency operation of the TP of the abdominal aorta, ablation and vascular prosthesis reconstruction. Intraoperative observation included a few hematocles in the abdominal cavity and retroperitoneal hemorrhage on the right side of the middle and inferior abdomen and the right iliac fossa. The right greater psoas muscle and the vertebral body were found to be eroded and destroyed, with the fractured bone being sharp. The retroperitoneal hematoma and the old organizing blood clot in the cavity was cleaned with total volume of approximately 2000 ml of normal saline. After the aortic wall was opened, the membrane of stent-graft could be seen as split, with a cresvase of about 1 cm. The periadiac necrotic tissue and bone chips were debrided. The operating field was washed repeatedly with iodophors saline and chlorhexidine. The abdominal aneurysm resection was performed with in situ placement of a prosthetic graft. The resected periaortic necrotic tissue was sent for pathological analysis. Analysis of the tissue sample showed florid necrotizing granulomas. The abdominal cavity was fitted with routine drainage tubes. The patient was treated with antitubercular drugs immediately after operation. The postoperative recovery was uneventful, and he was discharged two weeks later. Postoperative CT angiography was suggestive of the continuity of the abdominal aorta (Fig. 2d).

**DISCUSSION**

A TP of the abdominal aorta is exceedingly rare. Until recently, only two such cases could be traced in the Chinese-language literature. Han et al[8] reported that a patient suffered from multiple TP of abdominal aorta, and died of rupture of smaller abdominal aortic aneurysm and gastrointestinal hemorrhage after endovascular stent-graft exclusion. Zhao et al[9] outlined a case in which abdominal aortic aneurysm ablation and vascular prosthesis reconstruction were performed with exploratory laparotomy. In this report, we present our experience with two such patients and a brief review of pathogenesis, clinical features and management.

The two cases had the history of TB. Both complained of paroxysmal and radiating waist or abdominal pain. Other accompanying symptoms included intermittent low-grade fever and abdominal distension; nevertheless, neither presented with the manifestation of intestinal tract ischemia. Physical examination revealed a large abdominal pulsatile mass in one case, and an easily detectable non-pulsatile mass in the other. The mass pulsatility depended largely on the foundation of the pseudoaneurysm and communication between saccular mass and aorta. The final diagnosis was acquired based upon the history of TB, typical symptoms, and signs on CT or MRI. The two cases underwent combination of in situ reconstruction with a prosthetic graft and antitubercular therapy, and were well and asymptomatic at six-month follow-ups.

The majority of abdominal aortic pseudoaneurysms are due to trauma, infection[9], iatrogenic injury, and arteriosclerotic[7]. Aortic TP is extremely rare with a high mortality rate. Typical manifestation includes evidence of tuberculous focus or disseminated tuberculosis with one or more of the three clinical scenarios: 1) fever and persistent abdominal or back pain, 2) hypovolemic shock or other evidence of major bleeding, or 3) palpable or radiographically-visible periarterial mass, especially if expanding or pulsatile[8]. The Mycobacterium tuberculosis may encroach on the aortic wall in one of three ways. First, the bacilli may attach directly to the internal surface of the vessel wall. Normally, the aortic intima is very resistant to infection; however, when this protection is weakened by atherosclerotic plaque or aortic ulcers, the resistance to infection is depressed and the intimal surface may become colonized by blood-stream bacilli. Second, the bacilli may be carried to the adventitia or media by the vasa vasorum. Third, the bacilli are most commonly spread to the aorta by direct extension (or indirectly via the lymphatic system) from a contiguous focus, such as lymph nodes, paraspinal or posas abscess, vertebrae, and prostate[9]. The two cases presented herein were attributed to the extension of tuberculous infection in lymphatic system and the direct erosion from lumbar spinal TB. In fact, we postulated that all three infection routes may be implicated into the pathogenesis of TP of abdominal aorta. Caseating necrosis occurring in the entire layers of the aortic wall results in perforation, either with massive hemorrhage or with the formation of a perivascular hematoma. The latter may become encapsulated and retain communication with the lumen, in which case it is referred to as a pseudoaneurysm.

Early surgical operation in combination with perioperative antitubercular therapy has been demonstrated to offer favorable results for patient survival[10]. If the abdominal aortic aneurysm ruptures and results in hypotension, the success rate may be lower than 50%. Especially when the arteriae aorta is severely destroyed by TB, the rupture speed may be fairly fast[11]. Consequently, if a patient with an aortic...
TP develops symptoms of persistent abdominal or back pain, the surgical operation should be performed urgently\cite{12}. It needs to be noted here that the diameter of tuberculous false aneurysm is not a critical determinative factor for operation necessity\cite{13}. It is also not necessary to wait for enough antitubercular drugs, which would delay the opportunity to operate, since the curative effects of the antitubercular drugs on TB in the wall of TP and mural thrombosis are fairly limited\cite{14}.

The treatment for TP is in situ reconstruction using a prosthetic graft\cite{15}, extra-anatomic bypass re-establishment\cite{16}, and endovascular stent-graft repair\cite{17}. Controlling tuberculous infection and keeping distal aorta unobstructed are the most important therapeutic principles in surgical operation. The debridement of tuberculous focus and necrotic tissue and extra-anatomic bypass, such as the axillary – femoral artery bypass and avoidance of direct contact with tuberculous infection are commonly recommended\cite{16}. However, these procedures are known to provide a lower patency rate than in situ reconstruction. Despite the likelihood of prosthetic graft infection by tubercle bacillus, in our cases the in situ reconstruction did not carry a risk of infection as evidenced at follow-up; this is likely to be due to the patient having been provided adequate antitubercular drugs. In situ reconstruction depends on the size of aortic aneurysm and the condition of the neighboring aorta. After ablation of aortic aneurysm, the cutting edges of aorta and neighboring aortic wall should be evaluated. The surgeon should rely on visual inspection of the aortic wall to decide on the extent of resection, rather than on frozen sections and histological examination. Endovascular stent-graft repair of tuberculous aortic aneurysms has been reported in three cases with limited follow-up\cite{17}. Endovascular repair does not allow extensive debridement of the infected periarteric tissues, and thus could be associated with a high risk of infection and aneurysm recurrence, as occurred in one of the two cases in our report. Endovascular repair should be more suitable for patients with advanced age and poor health status, but long-term efficacy of this technique has not yet been established.

CONCLUSION

TP of the abdominal aorta carries a high risk of impending rupture. Once the diagnosis is made, operation should be performed urgently, even in the presence of a small pseudoaneurysm. A combination of in situ reconstruction with a prosthetic graft and antitubercular therapy offers favourable results for the treatment of TP of abdominal aorta.

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Case Report

Managing Anesthesia in a Patient of Osteogenesis Imperfecta: Practical Tips and Review of Literature

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ABSTRACT

Osteogenesis Imperfecta (OI) also known as “brittle bone disease” is an autosomal dominant disorder of the connective tissue associated with abnormalities of type 1 collagen leading to skeletal deformities with a characteristic tendency to fracture bones easily, and ocular, otologic, cutaneous and dental abnormalities. We hereby share an experience of anesthetic management of a 30-year-old man with OI with dislocation of cervical spine (C2 - C3) for correction, to emphasize the need for a detailed pre-anesthetic evaluation and preparation.

KEY WORDS: connective tissue disorders, difficult airway, fibreoptic intubation

INTRODUCTION

Airway management in a case of osteogenesis imperfecta (OI) patient coming for surgery is a major challenge for an anesthesiologist[1,2]. This is attributed to a short neck, large tongue, prominent occiput, fragile mandible and cervical spine and predisposition to odonto-axial dislocation, cervical vertebra and teeth fractures and mucosal bruising during laryngoscopy and intubation[3]. Fibreoptic intubation is an ideal technique in such situations, but if unavailable, an intubating laryngeal mask airway (ILMA) has also been recommended as it facilitates intubation with minimal neck movement. Patients with OI often undergo surgery, most frequently orthopedic. There are a number of important issues relating to the anesthetic management of these patients which are summarized in this article.

CASE REPORT

A 30-year-old male patient came with chief complaints of pain in the neck and stiffness since one year associated with tingling and numbness in both upper limbs. He had a history of frequent skeletal fractures for which he had under gone emergency closed reduction twice under general anesthesia, uneventfully.

There was no history of dyspnea on exertion, paroxysmal nocturnal dyspnea, chest pain, palpitation or syncope. There was no history of bleeding gums, GI bleed or easy bruising. On pre-anesthetic evaluation, he weighed 42 kilograms with height of five feet (60 inches). He had a characteristic blue sclera. The skeletal deformities included bilateral lower limb deformity in the form of genu valgus (knock knee), femur and tibia bow-shaped, bilateral dislocation of hip since childhood, with restricted hip abduction and extension and a waddling gait. He had no obvious kyphoscoliosis or any other vertebral abnormality, but there was increased lumbar lordosis.

Respiratory system revealed prominent ribs with restricted chest movements. Airway assessment revealed a short neck with restricted movements and pain. His dentition was firm and airway was Mallampati class- II. Spine was easily palpable and there was no associated spina-bifida. A chest X-ray showed crowding of rib with slanting and bilateral patchy opacities. A cardiology consult was done for the cardiac dysrythmia and a 2D-Echocardiography was done to rule out any valvular heart disease.

A MRI reported large posterior disc herniation, compression at C2 - C3 level, segmental hypertrophy, calcification and ossification over C2 - C3 level. His

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Resuscitation was initiated immediately but the patient could not be revived despite continued efforts for over an hour.

DISCUSSION

Airway management in an OI patient coming for surgery is a major challenge for an anesthesiologist. This is attributed to a short neck, large tongue, prominent occiput, fragile mandible and cervical spine. Associated basilar invagination, with an upward translocation of the cervical spine distorts the airway anatomy further. These patients frequently have associated congenital neurological and cardiovascular abnormality, the most common being valvular heart diseases in the form of mitral valve prolapse and aortic dissection[4,5].

There is a greater predisposition to pulmonary disease in patients of OI because of kyphoscoliosis and thoracic cage deformity, and recurrent aspirations requires aggressive preoperative optimization of lung function. There may also be hypoxemia secondary to ventilation-perfusion mismatch. Delay in extubation is anticipated in these patients for the same reason[6].

They are also clinically distinct by the presence of hypermetabolism[7]. Therefore, during anesthesia they may tend to develop malignant hyperthermia, although a direct relationship of OI to malignant hyperthermia is not substantiated[8]. Halothane and succinylcholine should be avoided in these patients; availability of rapid cooling methods is important.

Up to 30% incidence of bleeding diathesis in patients of OI has been reported[9]. Platelet dysfunction is common leading to bleeding disorder and easy bruisability. Increased capillary fragility, decreased levels of factor VIII and deficient collagen induced platelet aggregation has been implicated as causes for bleeding diathesis. An increase in intraoperative bleeding may occur despite normal bleeding times and coagulation values, accounting for the adequate arrangement of blood made in our case.

Patients with OI often undergo surgery, most frequently orthopedic. There are a number of important issues relating to the surgical and anesthetic management of these patients which can be summarized as follows:

1. The ease of fracture of bone and teeth;
2. Increased tendency to bleed secondary to platelet dysfunction and possible vascular disorders;
3. Increased tendency to develop malignant hyperthermia;
4. Difficulty in intubation as many patients may have short neck, large tongue and thoracic deformity; and
5. Gas exchange defects. Repeated respiratory infections are complications of OI
Regional anesthesia is difficult in patient with OI, due to skeletal abnormalities. Karabiyik et al have recommended total Intravenous anesthesia along with intubating LMA to manage elective cases\(^1\). Anticipating these problems helped us achieve a relatively uneventful intraoperative course in our patient. However, we were unprepared for the sudden and dramatic terminal events that we attribute to either an acute, extensive MI or a massive pulmonary embolism, neither of which could be confirmed since all our efforts were directed towards resuscitating the patient first. A third possibility of acute aortic dissection can also be considered. Later, a review of literature showed two reports of patients with OI without a known cardiac disease presenting with acute aortic dissection\(^{10,11}\). In the absence of confirmatory tests or autopsy, our diagnosis remains speculative but we now feel that a preoperative echocardiogram and venous Doppler of the lower limbs (in a bedridden patient like ours) could have helped.

**CONCLUSION**

In conclusion, we would like to emphasize the need for a detailed pre-anesthetic evaluation and preparation for anesthesia in a patient of OI. Special attention should be paid to exclude associated cardiovascular abnormalities, bleeding disorder, difficult airway or any other co-morbidity. An extra gentle care is essential in handling these patients to prevent the complications which can occur in the perioperative period like, fracture of bones and teeth, odontoaxial dislocation, occurrences of hyperthermia, and excessive bleeding. Proper positioning and adequate padding of all pressure points during surgery and transfer is required.

**REFERENCES**

Case Report

Sarcoidosis with Pulmonary Parenchymal Involvement and Co-existent Endobronchial Carcinoid

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ABSTRACT

Sarcoidosis and sarcoid reactions are associated with various malignancies such as Hodgkin lymphoma (HL), acute myeloid leukemia (AML), renal cell carcinoma (RCC), etc. Carcinoid tumors of colon, lung and kidneys co-existing with sarcoidosis are documented. Thyroid disorders were also found along with sarcoidosis and carcinoid tumors. Most of the case reports on concurrent lung carcinoid and sarcoidosis had non-metastatic carcinoid tumor and sarcoidosis without pulmonary parenchymal involvement. This is a case report of endobronchial typical carcinoid tumor with metastasis to regional lymph nodes co-existing with sarcoidosis having stage II disease. This case study concludes that there may be an association of endobronchial carcinoid tumor and sarcoidosis.

KEY WORDS: carcinoid tumor, lymphadenopathy, sarcoidosis,

INTRODUCTION

An association of sarcoidosis and malignancy has been a topic of controversy. "Malignancy-sarcoidosis syndrome"[1] and "malignancy-lymphoma syndrome"[2] are terms used by certain investigators because of their convincing association. Carcinoid tumor of lung[3,4], colon and kidneys which are associated with sarcoidosis are documented. The reported cases of co-existent lung carcinoid and sarcoidosis were non-metastatic carcinoid with no pulmonary parenchymal involvement[3,4]. This is a rare case of typical endobronchial carcinoid with lymph node metastasis co-existing with stage II sarcoidosis.

CASE REPORT

A 50-year-old woman was admitted with gall stones for cholecystectomy. Routine preoperative chest X-ray showed a right hilar lesion. The same lesion was noticed four years ago when a preoperative chest X-ray was taken prior to the thyroidectomy for multinodular goiter. Plain and contrast helical computed tomography (CT) scan showed 37 x 35 mm soft tissue density in right lung hilum with bilateral hilar and paratracheal lymphadenopathy and irregular thickening of bronchovascular bundles. Bronchial wash and brush cytology of the endobronchial growth showed features of a neuroendocrine tumor. Suspecting regional lymph node metastasis, a right pneumonectomy with regional lymph node removal was done. Gross examination of the surgical specimen showed a grayish-yellow tumor in the right bronchus measuring 40 x 38 mm (Fig. 1A). Microscopic examination showed typical carcinoid (Fig. 1B) which was positive for synaptophysin immunohistochemically (Fig. 1C). Four of the regional lymph nodes showed metastasis (Fig. 1D). Non-caseating granulomas were present within lung parenchyma (Fig. 1E) and also found in nine regional lymph nodes (Fig. 1F). Diagnosis of sarcoidosis with carcinoid was made. On further examination, she had no extrathoracic manifestations of sarcoidosis. The special stains, cultures for fungus and tuberculosis and Mantoux test were negative. The serum angiotensin-converting enzyme (ACE) level was 26.9 U/l (normal 6 - 52 U/l). The post - operative course of the patient was uneventful. On one and half years of follow-up, the patient is asymptomatic and doing well. No extrathoracic manifestations or new lesions of sarcoidosis became evident radiologically during this period.

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DISCUSSION

The association of sarcoidosis with various malignancies is described even though it remains controversial, whether it is true sarcoidosis or a sarcoïd-like reaction. Radiologically, bilateral hilar lymphadenopathy and pulmonary parenchymal involvement are features of stage II sarcoidosis[3]. In this case, the pulmonary parenchymal involvement

Fig. 1: A) Gross examination of grayish-yellow tumor in the right bronchus (arrow head shows tumor), B) Typical carcinoid tumor (H&E staining, x 40), C) Immunohistochemical staining of synaptophysin from pneumonectomy specimen (x 40), D) Regional lymph node metastasis (arrow heads, 1 lymph node, and 2 metastasis) (H&E staining, x 40), E) Non-casing granuloma in lung parenchyma (H&E staining, x 10), and F) Regional lymph nodes with multiple non-casing granuloma (H&E staining, x 10).
could be demonstrated microscopically. Levy et al showed a third association with thyroid disease in three out of seven patients(3). Multinodular goiter present in this patient can be ascribed to the embryological relationship of thyroid C cells (thyroid neuroendocrine cells) and carcinoid tumor cells both of which are postulated to originate from the neural crest(3). Serum ACE level reflects the activity of the disease(6). The normal serum ACE level in this patient could be because of an inactive disease. Radionuclide imaging with In-111 pentetetide and F-18 FDG PET helps to diagnose neuroendocrine tumors and sarcoidosis. Since, carcinoid tumors are neuroendocrine tumors they can be imaged with radiolabelled somatostatin analogs. Neuroendocrine tumors express somatostatin receptors. Sarcoidosis is intensely FDG-avid. Based on different patterns of radiotracer activity seen on In-111 pentetetide and F-18 FDG PET, it is now possible to differentiate regional metastatic carcinoid lymphadenopathy from a sarcoid lymphadenopathy(8). However, radionuclide imaging with In-111 pentetetide and F-18 FDG PET were not done to differentiate metastatic carcinoid lymphadenopathy from sarcoid lymphadenopathy in this case.

The possible mechanisms postulated for the disease association are 1) malignant disease may promote the onset of sarcoidosis either by causing local sarcoïd reaction that progress over time or by directly initiating all the manifestations of sarcoidosis as a systemic disease process(8) and 2) immunological abnormality in sarcoidosis may in some way promote onset of neoplasms(9). The probable mechanism in this patient could be the first cause since the patient had endobronchial carcinoid with sarcoidosis within the lung parenchyma and regional lymph nodes which can be ascribed to the persistence of endobronchial carcinoid for several years (more than four years after the first detection).

CONCLUSION

In conclusion, there may be an association between endobronchial carcinoid and sarcoidosis. The third benign thyroid disease association requires further studies. The staging process of lung carcinoid with regional lymphadenopathy should include imaging studies and biopsy confirmation to exclude sarcoidosis and sarcoïd reaction.

ACKNOWLEDGMENT

The author would like to thank Dr. Agnesamma Jacob, Professor and Head, Dr. Ramani KC, Professor, Department of Pathology, for their encouraging support and valuable technical advice. The author also gratefully acknowledges the valuable help of Dr. Ajith TA, Associate Professor, Department of Biochemistry, Amala Institute of Medical Sciences, during the preparation of this manuscript.

REFERENCES

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2014, 46 (1): 76 - 79

Construction of Anxiety and Dimensional Personality Model in College Students

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Psychol Rep 2013; 112:992-1004

A sample of 402 volunteer male (n = 156) and female (n = 246) Kuwaiti undergraduates responded to the Arabic versions of the Kuwait University Anxiety Scale and the Eysenck Personality Questionnaire. The latter questionnaire has four subscales: Psychoticism, Extraversion, Neuroticism, and Lie. Women obtained a higher mean score on Kuwait University Anxiety Scale and Neuroticism than did men, while men had a higher mean score on Psychoticism than did women. Factor analysis of the intercorrelations between the five variables, separately conducted for men and women, gave rise to two orthogonal factors called Anxiety-and-Neuroticism versus Extraversion, and Psychoticism versus Lie. Stepwise regression revealed that Neuroticism was the main predictor of anxiety. It was concluded that persons with high Neuroticism scores may be more vulnerable to anxiety than those with low scores.

Pathological Responses and Long-Term Outcome Analysis after Neoadjuvant Chemotherapy in Breast Cancer Patients from Kuwait Over a Period of 15 Years

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Ann Saudi Med 2013; 33:443-450

Background and Objectives: The attainment of pathological complete response (pCR) after neoadjuvant chemotherapy has been taken as a surrogate marker for disease-free survival and overall survival. This is however dependent on various other parameters such as stage, grade, and biologic markers.

Design and Settings: This is a retrospective study of 365 patients with histologically confirmed non-metastatic breast cancer patients treated with neoadjuvant chemotherapy at the Kuwait Cancer Control Centre from 1998 and 2009.

Patients and Methods: A total of 365 breast cancer patients who had received neoadjuvant chemotherapy from 1998-2009 were analyzed for the relationship of pCR with hormone status, Her2 status, histopathological subtype. Survival analysis was also conducted.

Results: Hormone receptor (HR) negative tumors had a higher pCR as against HR positive tumors, and the highest pCR in our analysis of pathological subtypes were seen in the HR+, Her2neu + and HR-, Her2neu + group. In our study, we could make out the paradoxes that well differentiated, and HR positive tumors had a better survival in spite of having lower pCR. The luminal A subtype also had a better overall survival than the triple negative subtype in spite of having lower pCR with neoadjuvant chemotherapy.

Conclusion: Though the achievement of pCR retains its significance, it is more prognostic in HR negative tumors. The importance of HR receptor status, grade, and histopathological subtype in the long-term survival has been emphasized.
Current Status and Future Trends in the Diagnosis and Treatment of Drug-Susceptible and Multidrug-Resistant Tuberculosis

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The global burden of tuberculosis (TB) is still large. The increasing incidence of drug-resistant, multidrug-resistant (MDR) (resistant to at least rifampicin and isoniazid), and extensively drug-resistant (XDR) (additionally resistant to a fluoroquinolone and kanamycin/amikacin/capreomycin) strains of Mycobacterium tuberculosis and the association of active disease with human immunodeficiency virus coinfection pose a major threat to TB control efforts. The rapid detection of M. tuberculosis strains and drug susceptibility testing (DST) for anti-TB drugs ensure the provision of effective treatment. Rapid molecular diagnostic and DST methods have been developed recently. Treatment of drug-susceptible TB is effective in ≥95% of disease cases; however, supervised therapy for ≥6 months is challenging. Non-adherence to treatment often results in the evolution of drug-resistant strains of M. tuberculosis due to mutations in the genes encoding drug targets. Sequential accumulation of mutations results in the evolution of MDR and XDR strains of M. tuberculosis. Effective treatment of MDR-TB involves therapy with 5 - 7 less effective, expensive, and toxic second-line and third-line drugs for ≥24 months and is difficult in most developing countries. XDR-TB is generally an untreatable disease in developing countries. Some currently existing drugs and several new drugs with novel modes of action are in various stages of development to shorten the treatment duration of drug-susceptible TB and to improve the outcome of MDR-TB and XDR-TB.

Profile of Lung Cancer in Kuwait

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Asian Pac J Cancer Prev 2013; 14:6181-6184

Background: Lung cancer is the most frequent cancer in males and the fourth most frequent site in females, worldwide. This study is the first to explore the profile of lung cancer in Kuwait.

Materials and Methods: Cases of primary lung cancer (Kuwaiti) in Kuwait cancer Registry (KCR) were grouped in 4 periods (10 years each) from 1970 - 2009. Epidemiological measures; age standardized incidence rate (ASIR) with 95% confidence intervals (CI), Standardized rate ratio (SRR) and Cumulative risk and Forecasting to year 2020 - 2029 used for analysis.

Results: Between years, 2000 - 2009 lung cancer ranked the 4th and the 9th most frequent cancer in males and females respectively. M:F ratio 1:3. Mean age at diagnosis (95%CI) was 65.2 (63.9-66.4) years. The estimated risk of developing lung cancer before the age of 75 years in males is 1.8% (1/56), and 0.6 (1/167) in females. The ASIR for male cases was 11.7, 17.1, 17.0, 14.0 cases/100,000 population in the seventies, eighties, nineties and in 2000 - 2009 respectively. Female ASIR was 2.3, 8.4, 5.1, 4.4 cases/100,000 population in the same duration. Lung cancer is the leading cause cancer death in males 168 (14.2%) and the fifth cause of death due to cancer in females accounting for 6.1% of all cancer deaths. The ASMR (95%CI) was 8.1 (6.6-10.0) deaths/100,000 population and 2.8 (1.3-4.3) deaths/100,000 population in males and females respectively. The estimated Mortality to incidence Ratio was 0.6.

Conclusions: The incidence of lung cancer between years 2000 - 2009 is not different from that reported in the seventies. KCR is expecting the number of lung cancer cases to increase.
Clinical Presentation and Management of Diabetes Mellitus in Pregnancy

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Objective: To evaluate the clinical presentation, management, and the outcome of diabetes mellitus in pregnancy.

Methods: One hundred seventy-one patients with diabetes mellitus admitted between September 1, 2006, and June 30, 2008, to the labor room at Maternity Hospital in Kuwait for induction of labor made up the study population; while an equivalent number of patients without medical complications who also were admitted for induction of labor made up the control group. The patients were assessed at admission, and their medical data were extracted. The study and control patients were monitored through labor/puerperium, and the outcome was documented.

Results: Gestational diabetes mellitus was diagnosed in 71.9% of the study patients, a past history of diabetes mellitus was recorded in 81.34% of the study patients, and 49.2% of the patients were admitted at 8 - 12 weeks of gestation for diabetic control. The mean weight gained in pregnancy was significantly higher for control patients (11.52 ± 5.643 versus [vs] 9.90 ± 5.757 kg/m(2); P <0.009), and the body mass index of study patients was higher (32.00 ± 6.160 vs 28.20 ± 5.885 kg/m(2); P <0.0001). Of the study population, 64.3% of the patients were managed with diet and increased physical activity and 35.7% with insulin, diet, and increased physical activity. The incidences of maternal morbidity in both study and control groups were comparable, and the incidence of preeclampsia was low, at 2.3%. The gestational age at delivery was higher in the control group (39.02 ± 1.834 weeks vs 38.62 ± 1.773 weeks; P <0.0001), and the percentage of cesarean deliveries was higher in the study population (44.4% vs 33.3%; P = 0.046). The Apgar scores of the both groups were comparable and in the normal range, and the incidences of fetal anomaly (1.17%), shoulder dystocia (1.8%), and Erb’s palsy (1.8%) were low.

Conclusion: Gestational diabetes mellitus was diagnosed in 71.9% of the diabetic patients studied, and dietary control and increased physical activity were the main modalities of management. There was an increased rate of cesarean section in the study population, the incidences of maternal and perinatal morbidity were low, and the perinatal outcomes were satisfactory.

Attitudes to Knee Osteoarthritis and Total Knee Replacement in Arab Women: A Qualitative Study

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BMC Res Notes 2013; 6:406

Background: Total Knee Arthroplasty (TKA) is offered to patients with knee osteoarthritis (OA) in the oil-rich countries in the Gulf region without adequate understanding of their perceptions, preferences or pain experiences. This study aimed to explore the pain experience and mobility limitation as well as the patient’s decision making process to undertake TKA among women with knee pain in the waiting list for surgery.

Methods: Five focus group discussions were conducted comprised of 39 women with severe knee OA
from the waiting list for TKA in the only orthopaedic hospital in Kuwait. Discussions were recorded, transcribed and coded for themes to identify the factors considered to be important in decision-making for TKA.

**Results:** Experiencing knee pain was central to daily living and affected patients and their families. Mobility limitation was shaped by a strong sense of expected obligation to take care of the family. Two major sources of TKA delay were identified; one was due to late clinical advice to undergo TKA which was the result of receiving several consultations from different clinicians each of whom tried the medical management for OA. The second delay occurred after the clinical advice for TKA and was mainly due to ambivalence of patients because of fear of the operation and the lack of information about TKA that resulted in unclear expectations of the surgery.

**Conclusions:** Both verbal and written information about TKA should be provided as part of preoperative rehabilitation. This is critical to improve doctor-patient interactions and facilitate informed decision about the procedure and thus achieve patient-centered healthcare.

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**An Outbreak of Mycobacterium abscessus Infection in a Pediatric Intensive Care Unit in Kuwait**


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**Pediatr Infect Dis J. 2013 Sep 13 [Epub ahead of print]**

**Background:** Mycobacterium abscessus has been associated with respiratory tract infections, localized skin and soft tissue infections and sepsis. However, outbreaks of M. abscessus are rare. AIM: to report an outbreak of M. abscessus causing respiratory tract infections in a Pediatric Intensive Care Unit (PICU) in Kuwait, its investigation and control measures.

**Methods:** Respiratory secretions, were obtained from ventilator dependent patients showing signs of sepsis, including fever, malaise and weight loss. The specimens were cultured on appropriate routine media. After the results of the sample taken from the index case as acid-fast bacilli positive, all patients were screened for M. abscessus carriage. Isolates were identified by INNO-LiPA Mycobacteria v2 line probe assay and DNA sequencing. Molecular fingerprinting DiversiLab strain typing was performed on the isolates. Epidemiologic investigation was conducted during the outbreak.

**Findings:** The outbreak affected five patients, four of whom had severe infections including one patient with septicemia. Asymptomatic carriage of outbreak strain was found in one patient. All environmental samples were negative for M. abscessus but some were positive for M. gordonae and M. fortuitum. The source could not be identified. Stringent infection control measures were put in place, including re-emphasizing hand hygiene and closure of the PICU to new admissions. A year later, no further case has occurred after the last case.

**Conclusion:** To our knowledge, this is the first report of a hospital-acquired outbreak of respiratory tract infection caused by M. abscessus in a PICU. In the absence of definite source identification, reinforcement of standard infection control guidelines was successful in containing the outbreak.
Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2014; 46 (1): 80 - 89

Recent Advances in **Transfusion Medicine**
Apr 1, 2014
_Ukraine / Lviv_
Contact: Kristina Zadorina, Kristina Zadorina, NBScience
Phone: 011-38-63-277-6465
Email: uk@nbscience.com

10th Annual **Asthma & COPD Conference**
Apr 2 - 3, 2014
_Untited Kingdom / London_
Contact: Fateja Begum, Delegate Co-ordinator, SMI Group
Phone: 011-44-20-7827-6000
Email: fbegum@smi-online.co.uk

**3rd International Congress on Epilepsy, Brain and Mind**
Apr 3 - 5, 2014
_Czech Republic / Brno_
Contact: Congress Secretariat, GUARANT International
Phone: 011-420-284-001-444
Email: ebm2014@guarant.cz

New Approaches to Prevention, Diagnosis & Treatment of Lung Diseases
Apr 3, 2014
_Ukraine_
Contact: Kristina Zadorina, Kristina Zadorina, NBScience
Phone: 011-38-63-277-6465
Email: uk@nbscience.com

New Technologies in **Surgical Dentistry & Maxillofacial Surgery**
Apr 3 - 4, 2014
_Ukraine / Kiev_
Contact: Kristina Zadorina, Kristina Zadorina, NBScience
Phone: 011-38-63-277-6465
Email: uk@nbscience.com

**Cardiovascular Outcomes in CKD: Problems & Solutions**
Apr 4 - 5, 2014
_Turkey / Antalya_
Contact: Prof. Dr. Gultekin Suleymanlar, President, Turkish Society of Nephrology
Fax: 011-90-24-2230-3028
Email: gauleymanlar@gmail.com

**1st Multidisciplinary Lung Cancer Management Course**
Apr 5 - 6, 2014
_India / Chandigarh_
Contact: Dr. CS Pramesh, Course Coordinator, Indian Society for Study of Lung Cancer
Phone: 011-91-172-275-6826
Email: cspramesh@gmail.com

MRCP Part 1 Revision Course
Apr 5 - 6, 2014
_Untited Kingdom / Glasgow_
Contact: Lorraine Hannah, Educational Events Administrator, Royal College of Physicians and Surgeons of Glasgow
Phone: 011-44-14-1227-3240
Email: Lorraine.Hannah@rcpsg.ac.uk

2014 Mid-Year Meeting of International Society for **Pharmacoepidemiology** (ISPE)
Apr 6 - 8, 2014
_Netherlands / Rotterdam_
Contact: ISPE
Phone: 301-718-6500; Fax: 301-656-0989
Email: ISPE@paimgmt.com

8th World Congress for **Neuro-Rehabilitation**
Apr 8 - 12, 2014
_Turkey / Istanbul_
Contact: Serenas Tourism
Phone: 011-90-312-440-5011; Fax: 011-90-312-441-4563
Email: info@wcnr2014.org

2014 World Psychiatric Association Regional Congress: Addressing Mental Health Needs in the Alps-Adria-Danube Region: Stigma, Community Based Care, **Stress & Suicidality**
Apr 9 - 12, 2014
_Slovenia / Ljubljana_
Contact: Congress Secretariat, GUARANT International
Phone: 011-420-284-001-444
Email: wpaljubljana2014@guarant.cz

7th International Conference on HPV, Polyomavirus and UV in **Skin Cancer**
Apr 9 - 12, 2014
_Italy / Novara_
Contact: Cinzia Borgogna, Event Secretariat
Phone: 011-39-3-2166-0582; Fax: 011-39-3-2162-0421
2014 Update in General Surgery
Apr 10 - 12, 2014
Canada / Ontario
Contact: Continuing Education and Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719
Email: info-SUR1304@cepdtoronto.ca

11th Biennial Canadian Orthopaedic Foot and Ankle Symposium
Apr 11 - 12, 2014
Canada / Ontario
Contact: Continuing Education and Professional Development, University of Toronto
Phone: 888-512-8173 or 416-978-2719
Email: info-SUR1405@cepdtoronto.ca

Tendon Transfers around the Shoulder
Apr 11, 2014
France / Toulouse
Contact: Groupe d'Etudes pour la Chirurgie osseuse
Phone: 011-33-389-360-532
Email: info@geco.asso.fr

18th Joint Meeting of World Association for Bronchology & Interventional Pulmonology / International Bronchoesophageology Society
Apr 13 - 16, 2014
Japan / Kyoto
Contact: Secretariat, Japan Convention Services
Phone: 011-81-3-3508-1214; Fax: 011-81-3-3508-1302
Email: wcipwcb2014@convention.co.jp

2nd Palliative Care Conference
Apr 13 - 15, 2014
Kuwait / Kuwait
Contact: D. Zakeer Ali Khan, Secretary, Palliative Care Center Kuwait
Phone: 965-2491-7507
Email: pckkw@hotmail.com

Emergency Medicine Mediterranean Cruise
Apr 15 - 26, 2014
Italy / Rome
Contact: Continuing Education, Inc, Meeting Planner, Continuing Education, Inc.
Phone: 800-422-0711 or 727-526-1571; Fax: 727-522-8304
Email: contactus@continuingeducation.net

7th Asian Pacific Congress of Heart Failure
Apr 17 - 19, 2014
Indonesia / Bali
Contact: Congress Secretariat, Indonesian Heart Association
Phone: 011-62-21-568-1149; Fax: 011-62-21-568-4220
Email: 7thapch@gmail.com

15th Dubai Spine Conference / 10th Pan Arab Spine Society Congress
Apr 19 - 22, 2014
United Arab Emirates / Dubai
Contact: Secretariat, Neuro Spinal Hospital
Fax: 011-971-4-342-9979
Email: spine@nshdubai.com

Relevant Topics in Anesthesia Essence of China Tour
Apr 19 - May 2, 2014
China / Beijing
Contact: Northwest Anesthesia Seminars
Phone: 800-222-6927; Fax: 509-547-1265

11th Annual Middle East Otolaryngology Conference & Exhibition: Head & Neck Surgery
Apr 20 - 22, 2014
United Arab Emirates / Dubai
Contact: Informa Life Sciences Exhibitions
Phone: 011-971-4-336-5161; Fax: 011-971-4-336-4021
Email: me-oto@informa.com

31st Annual MRI of the Head and Spine
Apr 21 - 23, 2014
United States / Nevada
Contact: Educational Symposia
Phone: 800-338-5901

Nephrology Dialysis Transplantation (NDT) Course for Reviewers-to-Be
Apr 23 - 24, 2014
Netherlands / Leiden
Contact: Kitty Jager, Local Coordinator, NDT Editorial Office
Phone: 011-31-20-566-7645; Fax: 011-31-20-691-9840
Email: k.j.jager@amc.uva.nl

12th Annual Conference of Association of Cutaneous Surgeons of India
Apr 24 - 26, 2014
India / Wayanad
Contact: Dr Febin K, Nodal Contact, Malabar Dermatology Club
Phone: 011-98-9582-9716

1st International Dental Implantology Conference
Apr 24 - 26, 2014
Poland / Warsaw
Contact: Gail Tito, Conference secretariat, Paragon Group
Phone: 011-41-22-533-0948; Fax: 011-41-22-580-2953
Email: secretariat@titanium-club-fti.com

2014 European Congress on Head & Neck Oncology
Apr 24 - 26, 2014
United Kingdom / London
Contact: Dion Bassett, APM, Kenes UK
Phone: 011-44-20-7383-8030
Email: echno@kenes.com
2014 World Congress on Osteoarthritis
Apr 24 - 27, 2014
France / Paris
Contact: Annemarie Kehler, Meeting & Registration Coordinator, Osteoarthritis Research Society International
Phone: 856-642-4429; Fax: 856-439-0525
Email: akehler@oarsi.org

16th Asian Musculoskeletal Society Meeting
Apr 25 - 26, 2014
China / Beijing
Contact: Fippa Fu, Registration Contact, China Golden Bridge Travel Service
Phone: 011-86-10-5281-8175
Email: Jstradiology@126.com

2014 American Society of Cataract & Refractive Surgery (ASCRS) Annual Symposium & Congress
Apr 25 - 29, 2014
United States / Massachusetts
Contact: ASCRS
Phone: 703-591-2220; Fax: 703-591-0614

4th Annual BIT World Congress of Molecular & Cell Biology
Apr 25 - 28, 2014
China / Dalian
Contact: Judy Du, BIT Congress, Inc.
Phone: 011-86-411-8479-9609 ext. 856; Fax: 011-86-411-8479-9629
Email: Judy@cmeb-congress.com

6th Annual BIT World Congress of Vaccine
Apr 25 - 28, 2014
China / Dalian
Contact: Rebecca Yu, Organizing Committee of WCV-2014, BIT Congress Inc., China
Phone: 011-86-411-8457-5669 ext. 860; Fax: 011-86-411-8479-9629
Email: rebecca@vaccinecon.com

9th European International Kidney Cancer Symposium
Apr 25 - 26, 2014
Ireland / Dublin
Contact: NIU Outreach
Email: outreachregistration@niu.edu

7th World Asthma, Allergy & COPD Forum
Apr 26 - 29, 2014
United States / New York
Contact: Congress Secretariat, World Immunopathology Organization
Phone: 011-7-495-735-1414; Fax: 011-7-495-735-1441
Email: info@wipocis.org

Novel Approaches for Complex Valvular Heart Disease
Apr 26, 2014
United States / Illinois
Contact: Blair Parker, Center for Continuing Medical Education, University of Chicago
Phone: 773-834-5418
Email: bparker@medicinebsd.uchicago.edu

2014 Human Genome Meeting: Genome Variation and Human Health
Apr 27 - 30, 2014
Switzerland / Geneva
Contact: MCI Geneva
Phone: 011-41-22-339-9721; Fax: 011-41-22-339-9631
Email: hgm2014reg@mci-group.com

2014 International Symposium on Biomedical Imaging
Apr 28 - May 2, 2014
China / Beijing
Contact: Institute of Electrical and Electronics Engineers
Email: D.bernstein@ieee.org

5th Annual Congress of Kazakhstan Oncologists & Radiologists
Apr 29 - 30, 2014
Kazakhstan / Almaty City
Contact: Nazgul Omarbayeva, Kazakh Science Institute of Oncology and Radiology, Kazakh Science Institute of Oncology and Radiology
Phone: 011-7-70-5130-7339; Fax: 011-7-72-7292-5577
Email: nazgulek87@mail.ru

10th Turkish German Gynecology Congress
Apr 30 - May 4, 2014
Turkey / Antalya
Contact: Rauf Kinay, Congress Project Leader, Opteamist Tourism & Organization
Phone: 011-90-216-414-1111; Fax: 011-90-216-414-6544
Email: tajev2014@opteamist.com

2014 Arteriosclerosis, Thrombosis & Vascular Biology Scientific Sessions
May 1 - 3, 2014
Canada / Ontario / Toronto
Contact: Convention Data Services
Phone: 866-639-7214 or 508-743-8528; Fax: 508-743-9680
Email: heartconferences@xpressreg.net

2014 Singapore Allergy & Rhinology Course & 1st SARC FESS Workshop
May 1 - 4
Singapore / Singapore
Contact: Tan Ee Sia, events360
Phone: 011-65-6618-2235
Email: register@events360.com.sg
16th European Congress of Endocrinology
May 3 - 7, 2014
Poland / Wroclaw
Contact: ECE 2014 Congress Secretariat, Bioscientifica
Phone: 011-44-14-5464-2240; Fax: 011-44-14-5464-2222
Email: ece2014@endocrinology.org

24th Biennial Congress of the European Society of Pediatric Neurosurgery
May 4 - 7, 2014
Italy / Rome
Contact: ERASMUS S.A, ESPN Administrative Secretariat & Congress Organizing Bureau, Erasmus Conferences Tours & Travel S.A.
Phone: 011-30-210-741-4700 (call center); Fax: 011-30-210-725-7532
Email: info@espncongress2014.org

7th World Congress on Pediatric Intensive and Critical Care
May 4 - 7, 2014
Turkey / Istanbul
Contact: Adina Siperman, APM, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: picc@kenes.com

1st Newcastle Cadaveric Endocrine Surgery Course
May 6 - 7, 2014
United Kingdom / Newcastle upon
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

7th World Congress of the World Institute of Pain
May 7 - 10, 2014
Netherlands / Maastricht
Contact: Niels Fundter, 7th World Congress of the World Institute of Pain, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: wip2014@kenes.com

18th ESH - EBMT Training Course on Haemopoietic Stem Cell Transplantation
May 8 - 11, 2014
Austria / Vienna
Contact: Nicolas Jaillard, Conference Coordinator, European School of Haematology
Phone: 011-33-1-5727-6833; Fax: 011-33-1-5727-6838
Email: nicolas.jaillard@univ-paris-diderot.fr

2014 Euro Spine Spring Specialty Meeting: Lumbar Degenerative Disorders
May 8 - 9, 2014
Czech Republic / Prague
Contact: Judith Reichert Schild, EUROSPINE, the Spine Society of Europe
Phone: 011-41-44-994-1404; Fax: 011-41-44-994-1403
Email: info@eurospine.org

2014 IMPAKT Breast Cancer Conference
May 8 - 10, 2014
Belgium / Brussels
Contact: Nicole Bullo, European Society for Medical Oncology
Phone: 011-41-91-973-1939; Fax: 011-41-91-973-1918
Email: impakt.registration@esmo.org

7th International Conference on Thrombosis & Hemostasis Issues in Cancer
May 9 - 11, 2014
Italy / Bergamo
Contact: Organizing Secretariat, SERVIZI C.E.C. S.r.l.
Email: info@icthic.com

Internal Derangements of Joints
May 9 - 11, 2014
Netherlands / Amsterdam
Contact: Wendy, Office Manager, iiCME
Phone: 205-467-0290; Fax: 205-467-0195
Email: iiicmemail@gmail.com

Core Skills in Hand Surgery
May 12 - 14, 2014
United Kingdom / London
Contact: Royal College of Surgeons of England
Phone: 011-44-20-7869-6300
Email: education@rcseng.ac.uk

Medical Management of Blood Pressure and Lipids
May 12 - 14, 2014
United Kingdom / London
Contact: Centre for Continuing Professional Development, Imperial College London
Phone: 011-44-20-7594-6882
Email: cpd@imperial.ac.uk

2014 Annual International Conference of Association of Psychology & Psychiatry for Adults & Children (APPAC)
May 13 - 16, 2014
Greece / Athens
Contact: APPAC Secretariat
Phone: 011-30-210-684-2663; Fax: 011-30-210-684-2079
Email: congress@appac.gr

Balloon Sinuplasty Course
May 13, 2014
United Kingdom / Newcastle
Contact: Michael Lobban, Newcastle Surgical Training Centre
Phone: 011-44-19-1223-1264; Fax: 011-44-19-1223-7248
Email: mlobban@ITSJNJ.com
<table>
<thead>
<tr>
<th>Event</th>
<th>Location</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2014 London Dermatopathology Symposium</strong></td>
<td>United Kingdom / London</td>
<td>Contact: London Dermatopathology Teaching Phone: 011-44-16-1980-8882 Email: <a href="mailto:info@londondermpath.com">info@londondermpath.com</a></td>
</tr>
<tr>
<td><strong>Anticoagulation in Emergency Care</strong></td>
<td>United Kingdom / London</td>
<td>Contact: Kerry Tarrant, Programme Director, Healthcare Conferences UK Phone: 011-44-19-3242-9933; Fax: 011-44-20-8181-6491 Email: <a href="mailto:kerry@hc-uk.org.uk">kerry@hc-uk.org.uk</a></td>
</tr>
<tr>
<td><strong>2014 Korea International Gastric Cancer Week</strong></td>
<td>South Korea / Daejeon Gastroenterology</td>
<td>Contact: Danny D. Jung, Secretariat Office Manager, IB Planning Phone: 011-82-2-2273-8551; Fax: 011-82-2-2273-7651 Email: <a href="mailto:kgca@ibmed.co.kr">kgca@ibmed.co.kr</a></td>
</tr>
<tr>
<td><strong>2nd Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity &amp; Hypertension</strong></td>
<td>Thailand / Bangkok</td>
<td>Contact: Congress Secretariat, ComtecMed Email: <a href="mailto:codhyap@codhy.com">codhyap@codhy.com</a></td>
</tr>
<tr>
<td><strong>21st Annual International &quot;Stress and Behavior&quot; Neuroscience &amp; Biopsychiatry Conference</strong></td>
<td>Russia / St. Petersburg</td>
<td>Phone: 240-899-9571 Email: <a href="mailto:isbs.congress@gmail.com">isbs.congress@gmail.com</a></td>
</tr>
<tr>
<td><strong>2014 Heart Failure</strong></td>
<td>Greece / Athens</td>
<td>Contact: European Society of Cardiology Phone: 011-33-4-9294-7600; Fax: 011-33-4-9294-8622</td>
</tr>
<tr>
<td><strong>8th Copenhagen Workshop on Carcinoma in situ and Germ Cell Cancer</strong></td>
<td>Denmark / Copenhagen</td>
<td>Contact: CIS Workshop Email: <a href="mailto:info@cis-workshop.dk">info@cis-workshop.dk</a></td>
</tr>
<tr>
<td><strong>Pharmacotherapy &amp; Surgical Treatment in Otorhinolaryngology</strong></td>
<td>Ukraine / Kiev</td>
<td>Contact: Kristina Zadorina, Kristina Zadorina, NBScience Phone: 011-38-63-277-6465 Email: <a href="mailto:uk@nbscience.com">uk@nbscience.com</a></td>
</tr>
<tr>
<td><strong>2014 International Symposium HIV &amp; Emerging Infectious Diseases</strong></td>
<td>France / Marseille</td>
<td>Contact: Secretariat, Overcome Phone: 011-33-1-4088-9797; Fax: 011-33-1-4641-0521 Email: <a href="mailto:isheid@overcome.fr">isheid@overcome.fr</a></td>
</tr>
<tr>
<td><strong>2014 Obstetric Anaesthesia</strong></td>
<td>Ireland / Dublin</td>
<td>Contact: Obstetric Anaesthetists’ Association Phone: 011-44-20-7631-8883; Fax: 011-44-20-7631-4352</td>
</tr>
<tr>
<td><strong>2014 Leading Innovative Vascular Education (LIVE)</strong></td>
<td>Greece / Athens</td>
<td>Contact: Secretariat, Conferre Ltd. Phone: 011-30-26-5106-8610; Fax: 011-30-26-5106-8610 Email: <a href="mailto:info@conferre.gr">info@conferre.gr</a></td>
</tr>
<tr>
<td><strong>2014 Malaysian Endocrine &amp; Metabolic Society Annual Congress</strong>: MAC 2014</td>
<td>Malaysia / Penang</td>
<td>Contact: Marcus Email: <a href="mailto:mac2014@console.com.my">mac2014@console.com.my</a></td>
</tr>
<tr>
<td><strong>Laparoscopic Colorectal Cadaver Course</strong></td>
<td>Italy / Bologna</td>
<td>Contact: Jon Baines Tours Phone: 011-44-20-7223-5618; Fax: 011-44-20-7228-7290 Email: <a href="mailto:info@jonbainestours.co.uk">info@jonbainestours.co.uk</a></td>
</tr>
<tr>
<td><strong>RSM Section of Coloproctology - Bologna</strong></td>
<td>Italy / Bologna</td>
<td>Contact: Jon Baines Tours Phone: 011-44-20-7223-5618; Fax: 011-44-20-7228-7290 Email: <a href="mailto:info@jonbainestours.co.uk">info@jonbainestours.co.uk</a></td>
</tr>
<tr>
<td><strong>2014 International Workshop on Gastroenterology</strong></td>
<td>Turkey / Ankara</td>
<td>Contact: Seval Kayabolen, Secretariat, Scientific Cooperations Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571 Email: <a href="mailto:secretary@med-scoop.org">secretary@med-scoop.org</a></td>
</tr>
<tr>
<td><strong>2014 International Workshop on Pediatrics</strong></td>
<td>Turkey / Ankara</td>
<td>Contact: Seval Kayabolen, Secretariat, Scientific Cooperations Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571 Email: <a href="mailto:secretary@med-scoop.org">secretary@med-scoop.org</a></td>
</tr>
</tbody>
</table>
2014 International Workshop on Radiology
May 24 - 25, 2014
Turkey / Ankara
Contact: Seval Kayabolen, Secretariat, Scientific Cooperations
Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571
Email: secretary@med-scoop.org

4th World Congress of Total Intravenous Anaesthesia & Target Controlled Infusion
May 24 - 26, 2014
Bulgaria / Sofia
Contact: Barbara Melamed, APM, Kenes UK
Phone: 011-44-20-7383-8030
Email: tiva@kenes.com

International Review of Psychosis and Bipolarity
May 25 - 28, 2014
Greece / Athens
Contact: Julie Ribeiro, Registrations Manager, Cortex Congress
Phone: 011-351-9-2624-3401
Email: jr@cortexcongress.com

Tropical Diseases
May 25 - 27, 2014
Canada / Quebec / Montreal
Contact: Isabel Stengler, Project Manager, IS Event Solutions
Phone: 450-550-3488, ext. 111; Fax: 514-227-5083
Email: isabel@iseventssolutions.com

15th World Congress for Cervical Pathology and Colposcopy
May 26 - 30, 2014
United Kingdom / London
Contact: Marie Blyte, APM, Kenes UK
Phone: 011-44-20-7383-8030
Email: ifcppc@kenes.com

Arab Paediatric Medical Congress
May 30 - 31, 2014
United Arab Emirates / Dubai
Contact: Dr. Doaa Said, Conference Director, Maarefah Management
Phone: 011-971-50-455-8738
Email: info@arabpeditriccongress.com

Epilepsy in Adults with Intellectual & Developmental Disabilities
May 30, 2014
United States / New York
Contact: Maria Mercado, Continuing Medical Education, NYU Langone Medical Center
Phone: 212-263-5295; Fax: 212-263-5293
Email: maria.mercado@nyumc.org

2014 Joint Congress of European Neurology
May 31 - Jun 3, 2014
Turkey / Istanbul
Contact: Congrex Switzerland
Phone: 011-41-61-686-7777; Fax: 011-41-61-686-7788
Email: istanbul2014@congrex.com

82nd European Atherosclerosis Society Congress
May 31 - Jun 3, 2014
Spain / Madrid
Contact: Rene Chait, APM, Kenes International
Phone: 011-41-22-908-0488; Fax: 011-41-22-906-9140
Email: eas@kenes.com

4th International Meeting Challenges in Endourology & Functional Urology
Jun 1 - 3, 2014
France / Paris
Contact: Erasmus S.A.
Phone: 011-30-210-741-4700; Fax: 011-30-210-725-7532
Email: challenges@challenges-endourology.com

Medical Retina
Jun 2 - 6, 2014
Switzerland / Lugano
Contact: European School for Advanced Studies in Ophthalmology
Phone: 011-41-91-921-1154

2014 International Workshop on Cardiology & Cardiothoracic Surgery
Jun 3 - 4, 2014
Turkey / Ankara
Contact: Seval Kayabolen, Secretariat, Scientific Cooperations
Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571
Email: secretary@med-scoop.org

2014 International Workshop on Neurology
Jun 3 - 4, 2014
Turkey / Ankara Oncology
Contact: Seval Kayabolen, Secretariat, Scientific Cooperations
Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571
Email: secretary@med-scoop.org

2014 International Workshop on Oncology
Jun 3 - 4, 2014
Turkey / Ankara Oncology
Contact: Seval Kayabolen, Secretariat, Scientific Cooperations
Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571
Email: secretary@med-scoop.org
41st Annual Meeting of International Society for the Study of the Lumbar Spine (ISSLS)
Jun 3 - 7, 2014
South Korea / Seoul
Contact: Katarina Olinder Eriksson, Administrator, ISSLS
Phone: 011-46-31-786-4436
Email: katarina.olinder@gu.se

International Course on Metabolic & Nutritional Issues in the ICU
Jun 3 - 4, 2014
Belgium / Brussels
Contact: Dominique Szyke, Department of Intensive Care Emergency Medicine, Erasme University Hospital, Université Libre de Bruxelles
Phone: 011-32-2-555-3694
Email: d.szyke@intensive.org

2014 Joint International Congress of International Liver Transplantation Society (ILTS), ELITA & Liver Intensive Care Group of Europe
Jun 4 - 7, 2014
United Kingdom / London
Contact: ILTS
Phone: 856-439-0500; Fax: 856-439-0525
Email: ilts@ils.org

2014 Rome Breast Surgery Symposium
Jun 4 - 6, 2014
Italy / Rome
Contact: Michela, AlfaFCM, AlfaFCM
Phone: 011-39-68-775-7099; Fax: 011-39-68-775-8886
Email: secretariat@romebreastsurgery.it

2014 International Breast Ultrasound Seminar (IBUS)
Greece
Jun 5 - 7, 2014
Greece / Athens
Contact: IBUS Secretariat
Email: info@ibus.org

2014 Transcatheter Valve Therapies
Jun 5 - 7, 2014
Canada / British Columbia / Vancouver
Contact: Cardiovascular Research Foundation
Phone: 646-434-4386

Pulmonary Hypertension and Pulmonary Vascular Disease
Jun 5 - 7, 2014
Switzerland / Lausanne
Contact: European Respiratory Society
Fax: 011-41-21-213-0100; Email: school@ersnet.org

World Psychiatric Association Thematic Conference: Neurobiology & Complex Treatment of Psychiatric Disorders & Addiction
Jun 5 - 7, 2014
Poland / Warsaw
Contact: Conference Secretariat, GUARANT International
Phone: 011-420-284-001-444; Fax: 011-420-284-001-448
Email: wpatcwarsaw2014@guarant.cz

2014 International Workshop on Anesthesiology
Jun 7 - 8, 2014
Aruba / Aruba
Contact: Seval Kayabolen, Secretariat, Scientific Cooperations
Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571
Email: secretary@med-scoop.org

2014 International Workshop on Dermatology
Jun 7 - 8, 2014
Turkey / Ankara
Contact: Seval Kayabolen, Secretariat, Scientific Cooperations
Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571
Email: secretary@med-scoop.org

2014 International Workshop on Orthopedic Surgery
Jun 7 - 8, 2014
Turkey / Ankara
Contact: Seval Kayabolen, Secretariat, Scientific Cooperations
Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571
Email: secretary@med-scoop.org

2014 International Workshop on Plastic Surgery
Jun 7 - 8, 2014
Turkey / Ankara
Contact: Seval Kayabolen, Secretariat, Scientific Cooperations
Phone: 011-90-312-223-5570; Fax: 011-90-312-223-5571
Email: secretary@med-scoop.org

18th International Congress of Parkinson's Disease & Movement Disorders
Jun 8 - 12, 2014
Sweden / Stockholm
Contact: MDS Congress
Phone: 414-276-2145; Fax: 414-276-3349
Email: congress@movementdisorders.org

20th Annual Organization for Human Brain Mapping (OHBM) Meeting
Jun 8 - 12, 2014
Germany / Hamburg
Contact: OHBM
Phone: 952-646-2029; Fax: 952-545-6073
Email: info@humanbrainmapping.org
Surgical Retina  
Jun 9 - 13, 2014  
Switzerland / Lugano  
Contact: European School for Advanced Studies in Ophthalmology  
Phone: 011-41-91-921-1154

Paediatric Allergy  
Jun 11 - 12, 2014  
United Kingdom / London  
Contact: Centre for Continuing Professional Development, Imperial College London  
Phone: 011-44-20-7594-6882  
Email: cpd@imperial.ac.uk

20th ASEAN Federation of Cardiology Congress  
Jun 12 - 15, 2014  
Malaysia / Kuala Lumpur  
Contact: Congress Secretariat, Event Solution Management Sdn Bhd  
Phone: 011-60-3-7955-6608; Fax: 011-60-3-7956-6608

Neurology/Psychiatry for Primary Care  
Jun 12 - 15, 2014  
United States / California / Anaheim  
Contact: Medical Education Resources  
Phone: 800-421-3756 or 303-798-9682; Fax: 303-798-5731  
Email: info@mer.org

11th Stroke Update for Physicians  
Jun 13, 2014  
Canada / Ontario  
Contact: Office of Continuing Medical Education, University of Ottawa & the Ottawa Hospital  
Phone: 613-798-5555 ext. 16646; Fax: 613-761-5262

2014 International Breast Ultrasound Seminar (IBUS)  
Turkey  
Jun 15 - 17, 2014  
Turkey / Istanbul  
Contact: IBUS Secretariat  
Email: info@ibus.org

5th International Conference on Osteoimmunology: Interactions of the Immune & Skeletal Systems  
Jun 15 - 20, 2014  
Greece / Kos  
Contact: Aegean Conferences, Inc.  
Phone: 610-527-7630; Fax: 610-527-7631

Imaging in Budapest  
Jun 15 - 20, 2014  
Hungary / Budapest  
Contact: Office of Continuing Medical Education, University of California San Francisco  
Phone: 415-476-4251; Fax: 415-476-0318  
Email: info@ocme.ucsf.edu

Central Nervous System / MRI  
Jun 16 - 20, 2014  
Netherlands / Amsterdam  
Contact: Walter Rijsselaere, Erasmus Course on Magnetic Resonance Imaging  
Phone: 011-32-2-477-5322; Fax: 011-32-2-477-5362  
Email: walter.rijsselaere@uzbrussel.be

36th Asia Pacific Dental Congress  
Jun 17 - 19, 2014  
United Arab Emirates / Dubai  
Contact: Sharon Mascarinas, APM, Kenes Asia  
Phone: 011-66-2-748-7881; Fax: 011-66-2-748-7880  
Email: apdc2014@kenes.com

12th Annual Meeting of International Society for Stem Cell Research (ISSCR)  
Jun 18 - 21, 2014  
Canada / British Columbia  
Contact: ISSCR Headquarters  
Phone: 224-592-5700; Fax: 224-365-0004  
Email: isscr@isscr.org

Newcastle Septorhinoplasty Cadaver Course  
Jun 18 - 20, 2014  
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

2014 Amsterdam Foot & Ankle Course  
Jun 19 – 20, 2014  
Netherlands / Amsterdam  
Contact: Academisch Medisch Centrum, Universiteit van Amsterdam  
Email: congresorganisatie@amc.nl

5th International Conference on Tissue Engineering  
Jun 20 - 25, 2014  
Greece / Kos  
Contact: Aegean Conferences, Inc.  
Phone: 610-527-7630; Fax: 610-527-7631

Advances in Prostate Imaging & Ablative Treatment of Prostate Cancer  
Jun 20 - 21, 2014  
United States / New York  
Contact: Maria Mercado, Continuing Medical Education, NYU Langone Medical Center  
Phone: 212-263-5295; Fax: 212-263-5293  
Email: maria.mercado@nyumc.org
<table>
<thead>
<tr>
<th>Conference</th>
<th>Location</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Forthcoming Conferences and Meetings</strong></td>
<td></td>
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<tr>
<td><strong>March 2014</strong></td>
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</tr>
<tr>
<td><strong>Ultrasound for Regional Anesthesia</strong></td>
<td>Canada</td>
<td>Contact: Christine Drane, Departmental Administrator, Department of Anesthesia, Toronto Western Hospital Phone: 416-603-5118; Fax: 416-603-6494 Email: <a href="mailto:christine.drane@uhn.ca">christine.drane@uhn.ca</a></td>
</tr>
<tr>
<td><strong>Comprehensive One Day Cadaver Course</strong></td>
<td>United States / Missouri</td>
<td>Contact: Association of Interventional Pain Physicians Phone: 270-554-9412; Fax: 270-554-5394 Email: <a href="mailto:asipp@asipp.org">asipp@asipp.org</a></td>
</tr>
<tr>
<td><strong>29th CINP World Congress of Neuropsychopharmacology</strong></td>
<td>Canada / British Columbia</td>
<td>Contact: Congress Office, CPO-Hanser Service Phone: 011-49-40-670-8820; Fax: 011-49-40-670-3283 Email: <a href="mailto:cinp2014@cpo-hanser.de">cinp2014@cpo-hanser.de</a></td>
</tr>
<tr>
<td><strong>2014 Live Interventional Neuroradiology &amp; Neurosurgery</strong></td>
<td>France / Paris</td>
<td>Contact: Course Organizer, Europa Organisation Phone: 011-33-534-452-645; Fax: 011-33-561-420-009 Email: <a href="mailto:insc-linnc@europa-organisation.com">insc-linnc@europa-organisation.com</a></td>
</tr>
<tr>
<td><strong>3rd Annual Global Healthcare Conference</strong></td>
<td>Singapore</td>
<td>Contact: Conference Secretariat, Global Science and Technology Forum Phone: 011-656-327-0166 Email: <a href="mailto:info@globalthc-conf.org">info@globalthc-conf.org</a></td>
</tr>
<tr>
<td><strong>Ophthalmology in China &amp; Hong Kong</strong></td>
<td>China / Shanghai</td>
<td>Contact: Jon Baines Tours Phone: 011-44-20-7223-5618; Fax: 011-44-20-7228-7290 Email: <a href="mailto:info@jonbainestours.co.uk">info@jonbainestours.co.uk</a></td>
</tr>
<tr>
<td><strong>9th International Congress of Laparoscopic Colorectal Surgery</strong></td>
<td>France / Paris</td>
<td>Contact: International Society of Laparoscopic Colorectal Surgery Phone: 913-402-7102; Fax: 913-273-1140 Email: <a href="mailto:events@lp-etc.com">events@lp-etc.com</a></td>
</tr>
<tr>
<td><strong>International Scientific Conference on Probiotics and Prebiotics</strong></td>
<td>Hungary / Budapest</td>
<td>Contact: Organizing Secretariat, PAMIDA International Ltd. Phone: 011-421-91-785-8838; Fax: 011-421-41-400-0123 Email: <a href="mailto:info@probiotic-conference.net">info@probiotic-conference.net</a></td>
</tr>
<tr>
<td><strong>14th World Congress of Endoscopic Surgery</strong></td>
<td>France / Paris</td>
<td>Contact: European Association for Endoscopic Surgery Phone: 011-31-40-252-5288; Fax: 011-31-40-252-3102 Email: <a href="mailto:info@eaes.eu">info@eaes.eu</a></td>
</tr>
<tr>
<td><strong>16th ESMO World Congress on Gastrointestinal Cancer</strong></td>
<td>Spain / Barcelona</td>
<td>Contact: Imedex Phone: 800-233-0957 (US only) or 678-242-0906; Fax: 770-751-7334 Email: <a href="mailto:registration@imedex.com">registration@imedex.com</a></td>
</tr>
<tr>
<td><strong>2014 Imaging in Cardiovascular Interventions</strong></td>
<td>Germany / Frankfurt</td>
<td>Contact: Congress Organizer, cme4u Email: <a href="mailto:info@cme4u.org">info@cme4u.org</a></td>
</tr>
<tr>
<td><strong>5th World Congress on Biotechnology</strong></td>
<td>Spain / Valencia</td>
<td>Contact: Conference Secretariat, Omics Publishing Group Phone: 650-268-9744; Fax: 650-618-1414 Email: <a href="mailto:biotechnology2014@omicsonline.net">biotechnology2014@omicsonline.net</a></td>
</tr>
<tr>
<td><strong>12th Renal Failure Academy</strong></td>
<td>Romania / Sighetu Marmatiei</td>
<td>Contact: Prof. Dr. Adrian Covici, Local Coordinator, Romanian Society of Nephrology Phone: 011-40-721-280-246; Fax: 011-40-232-211-752 Email: <a href="mailto:accovic@gmail.com">accovic@gmail.com</a></td>
</tr>
<tr>
<td><strong>13th International Congress on Pediatric Pulmonology</strong></td>
<td>Belgium / Brugge</td>
<td>Contact: Anne Flore Bidart, Conference Secretariat, Paragon Group &amp; Mediaxa Phone: 011-33-4-9703-8597; Fax: 011-33-4-9703-8598 Email: <a href="mailto:cipp@cipp-meeting.com">cipp@cipp-meeting.com</a></td>
</tr>
</tbody>
</table>
3rd International Conference on **Nephrology & Therapeutics**  
Jun 26 - 27, 2014  
*Spain / Valencia*  
Contact: Conference Secretariat, Omics Publishing Group  
Phone: 650-268-9744; Fax: 650-618-1414  
Email: nephro-2014@omicsonline.net

6th International Workshop on Advances in the Molecular Pharmacology & Therapeutics of **Bone Disease**  
Jun 30 - July 3, 2014  
*United Kingdom / Oxford*  
Contact: Janet Crompton, Conference Organizer, The Old White Hart  
Phone: 011-44-14-5354-9929; Fax: 011-44-14-5354-8919

**Pain Management & Palliative Care** for Primary Care  
Jun 30 – Jul 2, 2014  
*United States / Florida*  
Contact: MCE Conferences, MCE Conferences, MCE Conferences  
Phone: 888-533-9031; Fax: 858-777-5588  
Email: info@mceconferences.com

**Total Laparoscopic Hysterectomy** & Advanced Hysteroscopic Surgery Masterclass  
Jun 30 - Jul 1, 2014  
*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

**Symposia at Sea** Head and Neck Imaging: What You Need to Know  
Jul 1 - 12, 2014  
*Greece / Athens*  
Contact: Educational Symposia  
Phone: 800-338-5901

2014 International Cartilage Repair Society (ICRS) Focus Meeting  
Jul 3 - 5, 2014  
*Switzerland / Zurich*  
Contact: Sandra Kessler, Secretariat, ICRS  
Phone: 011-41-44-503-7371; Fax: 011-41-44-503-7372  
Email: sandra.kessler@cartilage.org

**Infectious Disease Medicine** for Primary Care  
Jul 4 - 6, 2014  
*Canada / Ontario*  
Contact: Medical Education Resources  
Phone: 800-421-3756 or 303-798-9682; Fax: 303-798-5731  
Email: info@mer.org

13th International Congress on **Neuromuscular Diseases**  
Jul 5 - 10, 2014  
*France / Nice Neurology*  
Contact: Congress Office, MCO Congrès SAS  
Phone: 011-33-4-9509-3800; Fax: 011-33-4-9509-3801  
Email: contact@icnmd2014.org

International Conference on **Geriatrics & Gerontology**  
Jul 8 - 10, 2014  
*United States / Illinois*  
Contact: Conference Secretariat, Omics Publishing Group  
Phone: 650-268-9744; Fax: 650-618-1414  
Email: geriatrics2014-@omicsonline.net

**Anticoagulation** in Emergency Care  
Jul 9, 2014  
*United Kingdom / London General Medicine*  
Contact: Kerry Tarrant, Programme Director, Healthcare Conferences UK  
Phone: 011-44-19-3242-9933; Fax: 011-44-20-8181-6491  
Email: kerry@hc-uk.org.uk

International Society for Magnetic Resonance in Medicine (ISMRM) Workshop on **Motion Correction in MRI**  
Jul 11 - 14, 2014  
*Norway / Tromso*  
Contact: Melissa Martinez, Meetings Coordinator, ISMRM  
Phone: 510-841-1899; Fax: 510-841-2340  
Email: info@ismrm.org

4th International Conference on Clinical & Experimental Ophthalmology  
Jul 14 - 16, 2014  
*United States / Maryland / Baltimore*  
Contact: Conference Secretariat, Omics Publishing Group  
Phone: 650-268-9744; Fax: 650-618-1414  
Email: ophthalmology2014@omicsonline.net

**Primary Care: ECG & Arrhythmia Interpretation** with Focus on a Clinical Approach  
Jul 14 - 24, 2014  
*United Kingdom / Harwich*  
Contact: Continuing Education, Inc, Meeting Planner, Continuing Education, Inc.  
Phone: 800-422-0711; Fax: 727-522-8304

**Renal Biopsy** in Medical Diseases of the Kidneys  
Jul 16 - 19, 2014  
*United States / New York*  
Contact: Columbia CME, Columbia University College of Physicians & Surgeons  
Phone: 212-305-3334  
Email: cme@columbia.edu
WHO-Facts Sheet

1. Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
2. Climate Change and Human Health
3. Children: Reducing Mortality
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1. MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS (MERS-CoV)

Overview
Coronaviruses are a large family of viruses that cause illness in humans and animals. In people, coronaviruses can cause illnesses ranging in severity from the common cold to Severe Acute Respiratory Syndrome (SARS).

Middle East respiratory syndrome coronavirus (MERS-CoV)
The novel coronavirus, first detected in April 2012, is a new virus that has not been previously identified in humans. In most cases, it has caused severe disease. Death has occurred in about half of cases. There is very limited information on transmission, severity and clinical impact with only a small number of cases reported thus far. It was named by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses in May 2013.

Where are MERS-CoV infections occurring?
Ten countries have now reported cases of human infection with MERS-CoV. Cases have been reported in France, Germany, Italy Jordan, Qatar, Saudi Arabia, Sultanate of Oman, Tunisia, the United Arab Emirates, and the United Kingdom. All cases have had some connection (whether direct or indirect) with the Middle East. In France, Italy, Tunisia and the United Kingdom, limited local transmission has occurred in people who had not been to the Middle East but who had been in close contact with laboratory-confirmed or probable cases.

How widespread is MERS-CoV?
How widespread this virus may be is still unknown. WHO encourages Member States to continue to closely monitor for severe acute respiratory infections (SARI) and to carefully review any unusual patterns of SARI or pneumonia. WHO will continue to share information as it becomes available.

What are the symptoms of MERS-CoV?
Common symptoms are acute, serious respiratory illness with fever, cough, shortness of breath and breathing difficulties. Most patients have had pneumonia. Many have also had gastrointestinal symptoms, including diarrhoea. Some patients have had kidney failure. About half of people infected with MERS-CoV have died. In people with immune deficiencies, the disease may have an atypical presentation. It is important to note that the current understanding of illness caused by this infection is based on a limited number of cases and may change as we learn more about the virus.

What is the significance of the recent finding of MERS-CoV in a camel?
On 11 November 2013, the Ministry of Health of Saudi Arabia announced that MERS-CoV had been detected in a camel linked to a human case in Saudi Arabia. This finding is consistent with previously published reports of MERS-CoV reactive antibodies in camels, and adds another important piece of information to our understanding of MERS-CoV ecology. However, this finding does not necessarily implicate camels directly in the chain of transmission to humans. The critical question that remains about this virus is the route by which humans are infected, and the way in which they are exposed. Most patients who have tested positive for MERS-CoV had neither a human source of infection nor direct exposure to animals, including camels. It is still unclear whether camels, even if infected with MERS-CoV, play a role in transmission to humans. Further genetic sequencing

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and epidemiologic data are needed to understand the role, if any, of camels in the transmission of MERS CoV to humans.

How do people become infected with this virus?
We do not yet know how people become infected with this virus. Investigations are underway to determine the source of the virus, the types of exposure that lead to infection, the mode of transmission, and the clinical pattern and course of disease.

How is the virus being transmitted to humans?
We still do not know the answer to this question. It is unlikely that transmission of the MERS-CoV to people occurs through direct exposure to an infected camel, as very few of the cases have reported a camel exposure. More investigations are needed to look at the recent exposures and activities of infected humans. WHO is working with partner agencies with expertise in animal health and food safety, including FAO, OIE and national authorities, to facilitate these investigations. Many technical organizations are offering their expertise to assist ministries responsible for human health, animal health, food, and agriculture. Investigation protocols and guidelines for dealing with new cases are available on the WHO website.

Should people avoid contact with animals or animal products?
Because neither the source of the virus nor the mode of transmission is known, it is not possible to give specific advice on prevention of infection. Contact with any obviously sick animals (including birds) should be avoided, and basic hygiene measures taken, especially frequent hand washing and changing of clothes and shoes or boots, after handling animals or animal products. Sick animals should never be slaughtered for consumption. The consumption of raw or undercooked animal products, including milk and meat, carries a high risk of infection from a variety of organisms that might cause disease in humans. Animal products processed appropriately through cooking or pasteurization are safe for consumption but should also be handled with care, to avoid cross-contamination with uncooked foods. Other hygiene measures include avoiding unwashed fruits or vegetables, and drinks made without safe water.

Are bats the source of the virus?
MERS-CoV has recently been found to be genetically related to a virus identified in bats from Southern Africa. But there is no definitive evidence that MERS-CoV originates in bats.

Can the MERS-CoV persist in the environment?
Some types of environment are better suited for persistence of certain viruses but we still do not know exactly how well and under what conditions MERS-CoV may persist in the environment.

Can the virus be transmitted from person to person?
Yes. We have now seen multiple clusters of cases in which human-to-human transmission has occurred. These clusters have been observed in health-care facilities, among family members and between co-workers. However, the mechanism by which transmission occurred in all of these cases, whether respiratory (e.g. coughing, sneezing) or direct physical contact with the patient or contamination of the environment by the patient, is unknown. Thus far, no sustained community transmission has been observed.

Is there a vaccine or treatment for MERS-CoV?
No vaccine is currently available. Treatment is largely supportive and should be based on the patient’s clinical condition.

How many people have been infected by MERS-CoV?
Globally, from September 2012 to January 2014, WHO has been informed of a total of 178 laboratory-confirmed cases of infection with MERS-CoV, including 75 deaths.

Based on the current situation and available information, WHO encourages all Member States to continue their surveillance for severe acute respiratory infections (SARI) and to carefully review any unusual patterns.

Health care providers are advised to maintain vigilance. Recent travellers returning from the Middle East who develop SARI should be tested for MERS-CoV as advised in the current surveillance recommendations.

Patients diagnosed and reported to date have had respiratory disease as their primary illness. Diarrhoea is commonly reported among the patients and severe complications include renal failure and acute respiratory distress syndrome (ARDS) with shock. It is possible that severely immunocompromised patients can present with atypical signs and symptoms.

Health care facilities are reminded of the importance of systematic implementation of infection prevention and control (IPC). Health care facilities that provide care for patients suspected or confirmed with MERS-CoV infection should take appropriate measures to decrease the risk of transmission of the virus to other patients, health care workers and visitors.

Are health workers at risk from MERS-CoV?
Yes. Transmission has occurred in health-care facilities, including spread from patients to health-care providers. WHO recommends that health-care
workers consistently apply appropriate infection prevention and control measures.

What is WHO recommending that countries do?
WHO encourages all Member States to enhance their surveillance for severe acute respiratory infections (SARI) and to carefully review any unusual patterns of SARI or pneumonia cases. WHO urges Member States to notify or verify to WHO any probable or confirmed case of infection with MERS-CoV.

2. CLIMATE CHANGE AND HUMAN HEALTH

Climate change is a significant and emerging threat to public health, and changes the way we must look at protecting vulnerable populations. Overwhelming evidence shows that human activities are affecting the global climate. Climate change has serious implications for public health. Extreme weather events, variable climates that affect food and water supplies, ecosystem changes are all associated with global warming and pose health risks.

Climate and weather already exert strong influences on health: increased deaths in heat waves, and in natural disasters such as floods, as well as changing patterns of life-threatening vector-borne diseases such as malaria and other existing and emerging infectious diseases are observed.

Continuing climate change will affect, in profoundly adverse ways, some of the social and environmental determinants of health: food, air and water, according to WHO Director-General Dr Margaret Chan. Areas with weak health infrastructure – mostly in developing countries - will be the least able to cope without assistance to prepare and respond.

This fact file describes current and projected effects of climate change on health.

10 facts on climate change and health
1. Over the last 50 years, human activities – particularly the burning of fossil fuels – have released sufficient quantities of carbon dioxide and other greenhouse gases to affect the global climate. The atmospheric concentration of carbon dioxide has increased by more than 30% since pre-industrial times, trapping more heat in the lower atmosphere. The resulting changes in the global climate bring a range of risks to health, from deaths in extreme high temperatures to changing patterns of infectious diseases.

2. From the tropics to the arctic, climate and weather have powerful direct and indirect impacts on human life. Weather extremes – such as heavy rains, floods, and disasters like Hurricane Katrina that devastated New Orleans, USA in August 2005 – endanger health as well as destroy property and livelihoods. Approximately 600 000 deaths occurred worldwide as a result of weather-related natural disasters in the 1990s, some 95% of which took place in developing countries.

3. Intense short-term fluctuations in temperature can also seriously affect health – causing heat stress (hyperthermia) or extreme cold (hypothermia) – and lead to increased death rates from heart and respiratory diseases. Recent studies suggest that the record high temperatures in western Europe in the summer of 2003 were associated with a spike of an estimated 70 000 more deaths than the equivalent periods in previous years.

4. Pollen and other aeroallergen levels are also higher in extreme heat. These can trigger asthma, which affects around 300 million people. Ongoing temperature increases are expected to increase this burden.

5. Rising sea levels – another outcome of global warming – increase the risk of coastal flooding, and could cause population displacement. More than half of the world’s population now lives within 60 kilometres of shorelines. Floods can directly cause injury and death, and increase risks of infection from water and vector-borne diseases. Population displacement could increase tensions and potentially the risks of conflict.

6. More variable rainfall patterns are likely to compromise the supply of fresh water. Globally, water scarcity already affects four out of every 10 people. A lack of water and poor water quality can compromise hygiene and health. This increases the risk of diarrhoea, which kills approximately 2.2 million people every year, as well as trachoma (an eye infection that can lead to blindness) and other illnesses.

7. Water scarcity encourages people to transport water long distances and store supplies in their homes. This can increase the risk of household water contamination, causing illnesses.

8. Climatic conditions affect diseases transmitted through water, and via vectors such as mosquitoes. Climate-sensitive diseases are among the largest global killers. Diarrhoea, malaria and protein-energy malnutrition alone caused more than 3 million deaths globally in 2004, with over one third of these deaths occurring in Africa.

9. Malnutrition causes millions of deaths each year, from both a lack of sufficient nutrients to sustain
life and a resulting vulnerability to infectious diseases such as malaria, diarrhoea, and respiratory illnesses. Increasing temperatures on the planet and more variable rainfalls are expected to reduce crop yields in many tropical developing regions, where food security is already a problem.

10. Steps to reduce greenhouse gas emissions or lessen the health impacts of climate change could have positive health effects. For example, promoting the safe use of public transportation and active movement - such as biking or walking as alternatives to using private vehicles - could reduce carbon dioxide emissions and improve public health. They can not only cut traffic injuries, but also air pollution and associated respiratory and cardiovascular diseases. Increased levels of physical activity can lower overall mortality rates.

Global environmental change

Large-scale and global environmental hazards to human health include climate change, stratospheric ozone depletion, changes in ecosystems due to loss of biodiversity, changes in hydrological systems and the supplies of freshwater, land degradation, urbanization, and stresses on food-producing systems.

Appreciation of this scale and type of influence on human health requires a new perspective which focuses on ecosystems and on the recognition that the foundations of long-term good health in populations rely in great part on the continued stability and functioning of the biosphere’s life-supporting systems. It also brings an appreciation of the complexity of the systems upon which we depend.

Harmful effects of environmental change and ecosystem impairment on human health. (Fig 1)

Millennium Ecosystem Assessment (2005)

Protecting health from global environmental change requires management at many levels, from the social and economic drivers of environmental change, to the resulting hazards and exposures for human populations. WHO supports this linkage of environmental and health agendas, for example by providing health expertise into the UN Conventions on Climate Change, Biological Diversity and Desertification, and by advising the health sector on the necessary responses to address the health risks posed by large-scale environmental change.

Global environmental change processes that impact human health: Stratospheric ozone depletion, UV radiation and health

It has been recognized for several decades that the release of chlorofluorocarbons and other atmospheric pollutants depletes stratospheric ozone, which in turn increases human exposure to ultraviolet radiation, causing skin cancer and cataracts.

The recognition of direct effects on human health effects was a major stimulus to the Montreal Protocol, which acts to reduce emissions of pollutants that weaken the ozone layer. Although this international agreement is proving highly effective in reducing risks in the long term, UV radiation remains a health hazard.

The World Health Organization, and partner organizations - through the Intersun project - have

Fig1. Effects of environmental change and ecosystem impairment on human health
developed and promote the UV Index, a tool to inform and educate the public about sun protection.

Ultraviolet radiation
Ultraviolet (UV) radiation is part of the electromagnetic spectrum emitted by the sun. Whereas UVC rays (wavelengths of 100 - 280 nm) are absorbed by the atmospheric ozone, most radiation in the UVA range (315 - 400 nm) and about 10% of the UVB rays (280 - 315 nm) reach the Earth’s surface. Both UVA and UVB are of major importance to human health.

Small amounts of UV are essential for the production of vitamin D in people, yet overexposure may result in acute and chronic health effects on the skin, eye and immune system.

What is UV radiation?
Everyone is exposed to UV radiation from the sun and an increasing number of people are exposed to artificial sources used in industry, commerce and recreation. Emissions from the sun include visible light, heat and UV radiation.

The UV region covers the wavelength range 100-400 nm and is divided into three bands:
- UVA (315-400 nm)
- UVB (280-315 nm)
- UVC (100-280 nm).

As sunlight passes through the atmosphere, all UVC and approximately 90% of UVB radiation is absorbed by ozone, water vapour, oxygen and carbon dioxide. UVA radiation is less affected by the atmosphere. Therefore, the UV radiation reaching the Earth’s surface is largely composed of UVA with a small UVB component.

Environmental factors that influence the UV level
Sun height: The higher the sun in the sky, the higher the UV radiation level. Thus UV radiation varies with time of day and time of year, with maximum levels occurring when the sun is at its maximum elevation, at around midday (solar noon) during the summer months.

Latitude: The closer the equator, the higher the UV radiation levels.

Cloud cover: UV radiation levels are highest under cloudless skies. Even with cloud cover, UV radiation levels can be high due to the scattering of UV radiation by water molecules and fine particles in the atmosphere.

Altitude: At higher altitudes, a thinner atmosphere filters less UV radiation. With every 1000 metres increase in altitude, UV levels increase by 10% to 12%.

Ozone: Ozone absorbs some of the UV radiation that would otherwise reach the Earth’s surface. Ozone levels vary over the year and even across the day.

Ground reflection: UV radiation is reflected or scattered to varying extents by different surfaces, e.g., snow can reflect as much as 80% of UV radiation, dry beach sand about 15%, and sea foam about 25%.

Ozone depletion and UV-related health effects
Depletion of the ozone layer is likely to aggravate existing health effects caused by exposure to UV radiation, as stratospheric ozone is a particularly effective UV radiation absorber. As the ozone layer becomes thinner, the protective filter provided by the atmosphere is progressively reduced. Consequently, human beings and the environment are exposed to higher UV radiation levels, and especially higher UVB levels that have the greatest impact on human health, animals, marine organisms and plant life.

Computational models predict that a 10% decrease in stratospheric ozone could cause an additional 300,000 non-melanoma and 4500 melanoma skin cancers and between 1.6 and 1.75 million more cases of cataracts worldwide every year.

3. CHILDREN: REDUCING MORTALITY

Overview
A child’s risk of dying is highest in the neonatal period, the first 28 days of life. Safe childbirth and effective neonatal care are essential to prevent these deaths. 44% of child deaths under the age of five take place during the neonatal period.

KEY FACTS
- 6.6 million children under the age of five died in 2012.
- More than half of these early child deaths are due to conditions that could be prevented or treated with access to simple, affordable interventions.
- Leading causes of death in under-five children are pneumonia, preterm birth complications, birth asphyxia, diarrhoea and malaria. About 45% of all child deaths are linked to malnutrition.
- Children in sub-Saharan Africa are about over 16 times more likely to die before the age of five than children in developed regions.
- Preterm birth, intrapartum-related complications (birth asphyxia or lack of breathing at birth), and infections cause most neonatal deaths. From the end of the neonatal period and through the first five years of life, the main causes of death are pneumonia, diarrhoea and malaria. Malnutrition is the underlying contributing factor in about 45% of all child deaths, making children more vulnerable to severe diseases.

Who is most at risk?
Newborns: Nearly three million babies die every year in their first month of life and a similar number are stillborn. Within the first month, up to one half of
all deaths occur within the first 24 hours of life, and 75% occur in the first week. The 48 hours immediately following birth is the most crucial period for newborn survival. This is when the mother and child should receive follow-up care to prevent and treat illness.

Prior to birth, the mother can increase her child’s chance of survival and good health by attending antenatal care consultations, being immunized against tetanus, and avoiding smoking and use of alcohol.

Children are at greater risk of dying before age five if they are born in rural areas, poor households, or to a mother denied basic education. More than half of under-five child deaths are due to diseases that are preventable and treatable through simple, affordable interventions. Strengthening health systems to provide such interventions to all children will save many young lives. Malnourished children, particularly those with severe acute malnutrition, have a higher risk of death from common childhood illness such as diarrhoea, pneumonia, and malaria. Nutrition-related factors contribute to about 45% of deaths in children under five years of age.

### Prevention with vaccines

For some of the most deadly childhood diseases, such as measles, polio, diphtheria, tetanus, pertussis, pneumonia due to Haemophilus influenzae type B and Streptococcus pneumoniae and diarrhoea due to rotavirus, vaccines are available and can protect children from illness and death.

### 4. FOODBORNE TREMATODIASES

Foodborne trematodiases affect more than 56 million people throughout the world. They are caused by trematode worms (“flukes”), of which the most common species affecting humans are Clonorchis, Opisthorchis, Fasciola and Paragonimus.

### KEY FACTS

- At least 56 million people globally suffer from one or more foodborne trematodiases.
- People become infected through the consumption of raw fish, crustaceans or vegetables that harbour the parasite larvae.
- Foodborne trematodiases are most prevalent in South-East Asia and South America.
- Foodborne trematodiases result in severe liver and lung disease.
- Safe and effective medicines are available to prevent and treat foodborne trematodiases.
People become infected through the consumption of raw or poorly cooked food: fish, crustaceans and vegetables that harbour the minute larval stages of the parasites (see Table 1).

### Table 1: Epidemiological characteristics of foodborne trematodiases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Infectious agent</th>
<th>Acquired through consumption of</th>
<th>Natural final hosts of the infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonorchiasis</td>
<td>Clonorchis sinensis</td>
<td>Fish</td>
<td>Dogs and other fish-eating carnivores</td>
</tr>
<tr>
<td>Opisthorchiasis</td>
<td>Opisthorchis viverrini, O. felineus</td>
<td>Fish</td>
<td>Cats and other fish-eating carnivores</td>
</tr>
<tr>
<td>Fascioliasis</td>
<td>Fasciola hepatica, F. gigantica</td>
<td>Aquatic vegetables</td>
<td>Sheep, cattle and other herbivores</td>
</tr>
<tr>
<td>Paragonimiasis</td>
<td>Paragonimus spp.</td>
<td>Crustaceans (crabs and crayfish)</td>
<td>Cats, dogs and other crustacean-eating carnivores</td>
</tr>
</tbody>
</table>

#### Transmission

Foodborne trematodiases are zoonoses, i.e. they are naturally transmissible from vertebrate animals to people and vice versa. Direct transmission is however not possible, as the relevant causative parasites become infective only after having completed complex life-cycles that usually involve stages in intermediate, non-human hosts. The first intermediate host is in all cases a freshwater snail, while the second host differs: in clonorchiasis and opisthorchiiasis it is a freshwater fish, in paragonimiasis it is a crustacean, while fascioliasis does not require a second intermediate host. The final host is always a mammal.

People become infected when they ingest the second intermediate host that is infected with larval forms of the parasite. In the case of fascioliasis, people become infected when the larvae are ingested together with the aquatic vegetables to which they are attached (see Table 1 for details).

#### Epidemiology

In 2005, more than 56 million people worldwide were infected with foodborne trematodes and over 7000 people died. Cases of foodborne trematodiases have been reported from over 70 countries worldwide; however South-East Asia and South America are the most affected areas. In these regions, infections with foodborne trematodes represent a significant public health problem.

Within countries, transmission is often restricted to limited areas and reflects behavioural and ecological patterns, such as people’s food habits, methods of food production and preparation, and the distribution of the intermediate hosts. Information on the epidemiological status of foodborne trematode infections in Africa is largely missing. The economic impact of foodborne trematodiases is significant, and is mainly linked to losses in the expanding aquaculture industry due to restrictions on exports and reduced consumer demand.

#### Symptoms

The public health burden attributable to foodborne trematodiases is predominantly due to morbidity rather than mortality. Early and light infections often pass unnoticed, as they are asymptomatic or only scarcely symptomatic. Conversely, if the worm load is high, general malaise is common and severe pain can occur, especially in the abdominal region, and most frequently in the case of fascioliasis. Chronic infections are invariably associated with severe morbidity. Symptoms are mainly organ-specific and reflect the final location of the adult worms in the body.

In clonorchiasis and opisthorchiiasis, the adult worms lodge in the smaller bile ducts of the liver, causing inflammation and fibrosis of the adjacent tissues and eventually cholangiocarcinoma, a severe and fatal form of bile cancer. Both C. sinensis and O. viverrini, but not O. felineus, are classified as carcinogenic agents.

In fascioliasis, the adult worms lodge in the larger bile ducts and the gall bladder, where they cause inflammation, fibrosis, blockage, colic pain and jaundice. Liver fibrosis and anaemia are also frequent. In paragonimiasis, the final location of the worms is the lung tissue. They cause symptoms that can be confounded with tuberculosis: chronic cough with blood-stained sputum, chest pain, dyspnoea (shortness of breath) and fever. Migration of the worms is possible: cerebral locations are the most severe.

#### Prevention and control

Control of foodborne trematodiases aims to reduce the risk of infection and at controlling associated morbidity.

Veterinary public health measures and food safety practices are recommended to reduce the risk of infection, while, to control morbidity, WHO recommends improved access to treatment using safe and effective anthelmintic medicines (drugs that expel the worms).

Treatment can be offered through preventive chemotherapy or individual case-management. Preventive chemotherapy involves a population-based approach whereby everyone in a given region or area is given medicines, irrespective of their infection status; it is recommended in areas where large numbers of individuals are infected. Individual case-management involves the treatment of people with confirmed or suspected infection: this approach is more appropriate where cases are less clustered and where health facilities are available.
5. IMMUNIZATION COVERAGE

Overview

Immunization averts an estimated 2 to 3 million deaths every year from diphtheria, tetanus, pertussis (whooping cough), and measles. Global vaccination coverage - the proportion of the world’s children who receive recommended vaccines - has remained steady for the past few years. For example, the percentage of infants fully vaccinated against diphtheria-tetanus-pertussis (DTP3) has held steady at 83% for the last three years.

During 2012, about 110.6 million infants worldwide got three doses of DTP3 vaccine, protecting them against infectious diseases that can cause serious illness and disability or be fatal. By 2012, 131 countries had reached at least 90% coverage of DTP3.

KEY FACTS

- Immunization prevents illness, disability and death from vaccine-preventable diseases including diphtheria, measles, pertussis, pneumonia, polio, rotavirus diarrhoea, rubella and tetanus.
- Global vaccination coverage is holding steady.
- Immunization currently averts an estimated 2 to 3 million deaths every year.
- But an estimated 22.6 million infants worldwide are still missing out on basic vaccines.
- Current levels of access to recommended vaccines
  Haemophilus influenzae type b (Hib) causes meningitis and pneumonia. Hib vaccine was introduced in 184 countries by the end of 2012. Global coverage with three doses of Hib vaccine is estimated at 45%. Hepatitis B is a viral infection that attacks the liver. Hepatitis B vaccine for infants had been introduced nationwide in 181 countries by the end of 2012. Global coverage with three doses of hepatitis B vaccine is estimated at 79%.
  Human papillomavirus — the most common viral infection of the reproductive tract — can cause cervical cancer, and other types of cancer and genital warts in both men and women. Human papillomavirus vaccine was introduced in 45 countries by the end of 2012.
  Measles is a highly contagious disease caused by a virus, which usually results in a high fever and rash, and can lead to blindness, encephalitis or death. By the end of 2012, 84% of children had received one dose of measles vaccine by their second birthday, and 146 countries had included a second dose as part of routine immunization.
  Meningitis A is an infection that can cause severe brain damage and is often deadly. By the end of 2012— two years after its introduction—more than 100 million people in 10 of the 26 African countries affected by the disease had been vaccinated with the MenAfriVac vaccine, developed by WHO and PATH.

Mumps is a highly contagious virus that causes painful swelling at the side of the face under the ears (the parotid glands), fever, headache and muscle aches. It can lead to viral meningitis. Mumps vaccine had been introduced nationwide in 120 countries by the end of 2012.

Pneumococcal diseases include pneumonia, meningitis and febrile bacteraemia, as well as otitis media, sinusitis and bronchitis. Pneumococcal vaccine had been introduced in 88 countries by the end of 2012, and global coverage was estimated at 19%.

Polio is a highly infectious viral disease that can cause irreversible paralysis. In 2012, 84% of infants around the world received three doses of polio vaccine. Only three countries - Afghanistan, Nigeria and Pakistan - remain polio-endemic.

Rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world. Rotavirus vaccine was introduced in 41 countries by the end of 2012, and global coverage was estimated at 11%.

Rubella is a viral disease which is usually mild in children, but infection during early pregnancy may cause fetal death or congenital rubella syndrome, which can lead to defects of the brain, heart, eyes and ears. Rubella vaccine was introduced nationwide in 134 countries by the end of 2012.

Tetanus is caused by a bacterium which grows in the absence of oxygen, e.g., in dirty wounds or in the umbilical cord if it is not kept clean. It produces a toxin which can cause serious complications or death. The vaccine to prevent maternal and neonatal tetanus had been introduced in 103 countries by the end of 2012. An estimated 81% of newborns were protected through immunization. Maternal and neonatal tetanus persist as public health problems in 30 countries, mainly in Africa and Asia.

Yellow fever is an acute viral haemorrhagic disease transmitted by infected mosquitoes. As of 2012, yellow fever vaccine had been introduced in routine infant immunization programmes in 36 of the 48 countries and territories at risk for yellow fever in Africa and the Americas and coverage was estimated at 37%.

Key challenges

Despite improvements in global vaccine coverage during the past decade, there continue to be regional and local disparities resulting from:
- limited resources;
- competing health priorities;
- poor management of health systems; and
- inadequate monitoring and supervision.

In 2012, an estimated 22.6 million infants worldwide were not reached with routine immunization services, of whom more than half live in three countries: India, Indonesia and Nigeria.
Priority needs to be given to strengthening routine vaccination globally, especially in the countries that are home to the highest number of unvaccinated children. Particular efforts are needed to reach the underserved, especially those in remote areas, in deprived urban settings, in fragile states and strife-torn regions.

6. TEN FACTS ON OBESITY

Obesity has reached epidemic proportions globally, with at least 2.8 million people dying each year as a result of being overweight or obese. Once associated with high-income countries, obesity is now also prevalent in low- and middle-income countries.

1. Overweight and obesity are defined as “abnormal or excessive fat accumulation that may impair health”
Body mass index (BMI) – the weight in kilograms divided by the square of the height in meters (kg/m$^2$) – is a commonly used index to classify overweight and obesity in adults. WHO defines overweight as a BMI equal to or more than 25, and obesity as a BMI equal to or more than 30.

2. More than 1.4 billion adults were overweight in 2008, and more than half a billion obese
At least 2.8 million people each year die as a result of being overweight or obese. The prevalence of obesity has nearly doubled between 1980 and 2008. Once associated with high-income countries, obesity is now also prevalent in low- and middle-income countries.

3. Globally, over 40 million preschool children were overweight in 2008
Childhood obesity is one of the most serious public health challenges of the 21st century. Overweight children are more likely than non-overweight children to develop diabetes and cardiovascular diseases at a younger age, which in turn are associated with a higher chance of premature death and disability.

4. Overweight and obesity are linked to more deaths worldwide than underweight
65% of the world’s population live in a country where overweight and obesity kills more people than underweight. This includes all high-income and middle-income countries. Globally, 44% of diabetes, 23% of ischaemic heart disease and 7-41% of certain cancers are attributable to overweight and obesity.

5. For an individual, obesity is usually the result of an imbalance between calories consumed and calories expended
An increased consumption of highly calorific foods, without an equal increase in physical activity, leads to an unhealthy increase in weight.

6. Supportive environments and communities are fundamental in shaping people’s choices and preventing obesity
Individual responsibility can only have its full effect where people have access to a healthy lifestyle, and are supported to make healthy choices.

7. Children’s choices, diet and physical activity habits are influenced by their surrounding environment
Social and economic development as well as policies in the areas of agriculture, transport, urban planning, environment, education, food processing, distribution and marketing influence children’s dietary habits and preferences as well as their physical activity patterns. Promoting unhealthy weight gain leading to childhood obesity.

8. Eating a healthy diet can help prevent obesity
People can: 1. maintain a healthy weight, 2. limit total fat intake and shift fat consumption away from saturated fats to unsaturated fats. 3. increase consumption of fruit, vegetables, pulses, whole grains and nuts. 4. limit the intake of sugar and salt.

9. Regular physical activity helps maintain a healthy body
People should engage in adequate levels of physical activity throughout their lives. At least 30 minutes of regular, moderate-intensity physical activity on most days reduces the risk of cardiovascular disease, diabetes, colon cancer and breast cancer. Muscle strengthening and balance training can reduce falls and improve mobility among older adults. More activity may be required for weight control.

10. Curbing the global obesity epidemic requires a population-based multisectoral, multidisciplinary, and culturally relevant approach
WHO’s Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases provides a roadmap to establish and strengthen initiatives for the surveillance, prevention and management of noncommunicable diseases, including obesity.