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Continued inside

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Continued from cover

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Book

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Book chapter

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

Weblinks

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

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Editorial

History of Blood Pressure and Its Measurement

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"If you want to understand today, you have to search yesterday."

Pearl Buck

Measurement of arterial pressures started with the study of radial pulse by Charaka around 400 BC. This was copied by Hippocrates around 100 BC in Greece where the Samhitas had reached; brought along by the returning army of Alexander, the Great. The Egyptians, the Arabs and, the Chinese had also developed their own methods of the crude appreciation of the arterial pulse pressure. The three finger study of the pulse, originally described by Charaka, was endorsed by Hippocrates in his thesis. In the intervening 2500 years plenty of water has flowed down the Ganges River. None of those discoveries and innovations have yet unravelled the greatest mystery of how blood flows inside the blood vessels and how the heart, a small muscular pump weighing 300 grams, could pump blood into this huge sea of capillaries where even a small RBC has to squeeze itself through those very tiny tubes, requiring enormous energy! This process, if it is true, requires enormous energy for blood movement inside the closed system where the blood gets collected from the capillary swimming pool to be sent back to the same pool. The heart could be compared to a swimming pool pump! Many of us think that our generation is responsible for all the newer developments in this area. Reminds me of what an African Proverb once said: "Until lions have their historians, tales of the hunt shall always glorify the hunters."

The Beginning

Reverend Stephen Hales (1677 - 1761), who began the first enquiry into blood flow, in 1733 inserted a long glass tube into his mare's crural artery and saw blood running up the tube to a height of 8'4"! He continued to do many other physiological studies to be elected FRS in 1718 only to be followed by the French Royal Society in 1753. Thus began the present era of blood pressure measurement directly. Johannes Muller, a historian, once wrote that this discovery overshadowed even the discovery of blood itself in its impact on science. Poiseuille in 1828 introduced the mercury manometer but still we needed to puncture an artery to measure the pressure.

Ludwig's kymograph and Vierordt's counter pressure sphygmograph were further innovations. In the year 1860 Etienne Jules Marey brought in lots of newer innovations on the sphygmograph, which was further refined in London by a homeopath, RE Dudgeon. Pioneering its popular usage was achieved by Bourdon Sanderson who later went on to become the Regius Professor of Medicine at Oxford. It was Potain who suggested that all is not in order in this area and he brought in arterial resistance into the picture but was ignored by the majority of his peers.

Surgeon Faivre in 1856 was the first to use intra-arterial blood pressure measurement during surgery through a cannula. The story of non-invasive measurements started with Samuel Siegfried Karl Ritter von Basch in Vienna who in 1870 introduced an inflatable balloon but it was very complicated. Zadek, following on his predecessor, measured the intra-arterial pressures simultaneously to compare the two methods with success.

Gradual improvements have brought us to the present era which started in Turin, Italy in 1896 by Scipone Riva Roci. WH Lewis made some improvements but the present wider cuff was the invention of von Recklinghausen in 1911. All these could only measure the so called systolic pressure

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

recorded when the arterial lumen gets totally occluded. There was then a craze for recording the diastolic blood pressure which was given a boost by Hill and Bernard in London in 1897 and Underwood in 1962. But more than them all, it was the Russian surgeon from St. Petersburg, NC Korotkoff who for the first time noted that the brachial artery beyond the obstruction starts to emit loud sounds on auscultation at the level of the systolic pressure and further lowering of pressure changes the quality of sound that at one stage completely disappears. He called that pressure at which the Korotkoff's sounds completely disappear as the diastolic pressure.

The spin off of this discovery was the use of binaural stethoscope in place of Laennec's tube, or the so called uni-aural stethoscope. Dr. Seagull provides a nice translation of Korotkoff's article in the Russian Journal of Clinical Medicine 1956; volume 4 and number 11[1].

Later Developments

These days, sensors on the thumb, strain gauges, photocells, and even semiconductors seem to have joined the bandwagon for recording blood pressure more accurately; even for continuous monitoring. That said, I must hasten to add that there are a lot more new data in this area which are still shrouded in mystery as it was before Rev. Stephen Hales started his monumental work. For the beginning, it has been now discovered that the diastolic pressure cannot be easily recorded correctly as the Korotkoff's sounds cannot be easily discerned by all doctors and nurses. There are now more sounds described. Then came the bombshell from the largest study, the MRFIT study, where 500,000 people were screened to select 100,000 subjects for the study. The data, in retrospect, did reveal very clearly that the future events and complications, even death, depended ONLY on the systolic pressure and that the diastolic pressure has very little predictability[2].

The ascendency of the systolic over the diastolic pressure for prognosis is now an accepted fact. Progress in any area of science is change for the better. That is what is happening in this field as well. Our present status could be gauged by the frustration of one of the greatest researchers in this area, Professor Sir George Pickering, who studied this all his life. "More people make a living OFF blood pressure than dying OF it."[3] The abuse and misuse of the sphygmomanometer and the multiple attempts at lowering the "normal" range has caused untold misery to the common man. These attempts have kept pace with the exponential growth of the number of blood pressure lowering drugs from the industry! The history of this saga is very well documented in the beautiful book by Professor Jerg Blech, titled Disease Inventors."[4]

What is the future?

With the advent of progress in physics and fluid flow dynamics, our ideas of blood pressure and its measurement need refining, to say the least. The blood circulation happens in a closed tube system which is not linear and follows the laws of non-linear dynamics. The heart that we think is the kingpin in the game never existed in our fetal life for nearly 20 weeks and the blood circulated on its own around the body with the help of two dorsal tubes which later became part of the heart. Blood flow does not, therefore, totally depend on the heart's contractions![5]. Where does the enormous energy that we talked about earlier in the chapter come from for blood circulation? Recent data do show that the flowing blood generates its own energy as it flows in whirls and not in the way we have been taught in the medical school. Angioscopic studies have shown the whirling very clearly in animals as also in man.

How then are we keeping the definition of blood pressure as the "lateral pressure exerted on the vessel wall by the flowing blood"? Does flowing blood exert lateral pressure? Is it a simple laminar flow as happens in a straight tube? We need to audit our management strategies. Uffe Ravnskov had audited seventeen studies of blood pressure management in the world literature recently and has come up with startling data that the absolute risk reduction (ARR) of blood pressure lowering using chemical molecules was negligible![6]. There are more questions in this area than answers. Lot more needs to be done. Here comes the usefulness of the history of blood pressure measurement through the last 2500 years - understand today by studying yesterday!

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Review Article

Treatment of Depression during Pregnancy

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ABSTRACT

Women of child bearing age are at a high risk for depression. Despite the high incidence of depression during pregnancy and the postpartum period, guidelines for treating this depression are lacking. It is a challenge to treat the illness effectively and also to minimize risk to the fetus or the neonate. The safety of antidepressants during pregnancy is an unresolved issue and has made it difficult to choose the appropriate antidepressant to be used during pregnancy. In this review we have suggested some strategies that may be useful to the physicians.

KEY WORDS: antidepressants, postpartum, pregnancy

INTRODUCTION

The incidence of depression in women is two to three times more than men. The risk of depression in women parallels with the fluctuation of estrogen across life cycle. During puberty, premenstrual period, pregnancy, postnatal and perimenopausal period, women are highly vulnerable to depression[1]. The prevalence of depression during pregnancy and postpartum has been reported to be around 10%[2]. The treatment of depression during pregnancy and postpartum is a very complex and challenging task. It has been reported that 86% of pregnant women suffering from depression do not receive any treatment. Majority of women do not seek help because of the stigma associated with mental health services[3]. Once depression has been diagnosed during pregnancy or postpartum the decision to treat depression is still a dilemma[4]. The treatment of a depressed pregnant or postpartum woman is quite complicated as it may affect the growing fetus or breast feeding infant. On the other hand, untreated depression in pregnancy or postpartum could also have harmful effects both on the mother as well as the child. The knowledge about the consequences of using antidepressants during pregnancy is inadequate due to lack of randomized controlled trials[5] or systematic longitudinal studies[4]. This review suggests some guidelines that can be useful while treating depression during pregnancy.

RISK OF UNTREATED DEPRESSION DURING PREGNANCY

Depression during pregnancy can harm both the mother as well as the growing fetus. Untreated depression may lead to consequences like poor prenatal care, maternal weight gain and increased risk of intrauterine growth retardation, low birth weight and premature delivery [6]. The risk of relapse of depression during postpartum period is high if depression is not treated or medications are discontinued during pregnancy. Postpartum depression is one of the leading causes of suicide during this period. Postpartum depression can also result in poor maternal infant bonding, infanticide and unhealthy child development practices. Previous studies have shown that infants born to mothers suffering from depression had higher cortisol levels, which even continued through adolescence compared to children born to mothers who were not depressed[7]. However cortisol levels were normal in infants born to mothers who received antidepressants[7,8]. High cortisol levels are a risk factor for increased vulnerability to psychopathology. Hence discontinuation of antidepressants or failing to treat depression during pregnancy can lead to adverse outcomes [9].

RISKS OF TREATING DEPRESSION DURING PREGNANCY

The use of antidepressants during pregnancy and the choice of an appropriate antidepressant during pregnancy have been very controversial. The US Food and Drug Administration (FDA) categorizes antidepressants under pregnancy category C which includes drugs with adverse effects in animals and drugs for which there are no studies in humans. Major limitation of this is that there is poor discrimination between medications

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within the group and also between the groups of antidepressants[9].

The effect of antidepressants on pregnancy and on the fetus has been reported in a few prospective studies. Chambers *et al* reported that infants exposed to fluoxetine during pregnancy had a higher incidence of minor anomalies (defined as those with no cosmetic or functional importance) compared with those who were not exposed to fluoxetine[10]. However, other studies did not report an increased risk for the development of major physical anomalies in women who were exposed to tricyclic antidepressants(TCAs), fluoxetine or the newer selective serotonin reuptake inhibitors (sertraline, paroxetine and fluvoxamine)[11,12]. There is also no evidence that these antidepressants increase risk for intrauterine fetal death[13]. However, a recent study reported that women who had prior history of spontaneous abortions, received selective serotonin reuptake inhibitors (SSRI), bupropion[14] or mirtazapine during early pregnancy had a higher rate of spontaneous abortions[15-17]. A neonatal withdrawal syndrome was also seen in neonates born to women who continued fluoxetine during the third trimester, characterized by jitteriness, hypoglycemia, hypothermia, poor muscle tone, respiratory distress, weak or absent crying, desturation on feeding, low birth weight and shorter birth length[10]. Use of newer antidepressants like venlafaxine during pregnancy was also associated with increased incidence of preterm births, respiratory problems, low Apgar scores, hypoglycemia and convulsions in neonates as seen with SSRI's[18,]. This syndrome is also known as poor neonatal adaptation or neonatal neurobehavioral syndrome[9]. This has also been reported with paroxetine, sertraline and citalopram[19- 21]. Though the exact reason is not known, three reasons have been hypothesized for this syndrome:

- Serotonergic toxicity (tremor, tachypnea, diaphoresis and irritability or agitation)
- Antidepressant discontinuation syndrome
- Immaturity of newborn's central nervous system[3]

It was suggested to lower the dosage or discontinue the antidepressant 10 to 14 days prior to delivery to minimize fetal load at birth. But it poses an increased risk for postpartum depression. The use of SSRI's during pregnancy was associated with an increased incidence of primary pulmonary hypertension in the newborn (PPHN). A comparison study of women whose infants were diagnosed with PPHN with women whose infants were not diagnosed with PPHN showed that 14 infants with PPHN were exposed to SSRI after the 20th week of gestation compared with six infants who did not have PPHN. This study was the basis for the black box warning regarding the association of PPHN with SSRI's. However prospective studies are required to confirm the finding[9]. PPHN was also reported with some serotonin and norepinephrine reuptake inhibitors (SNRI) used in late gestation[22].

There is a controversy regarding use of paroxetine during pregnancy. One study reported that women exposed to paroxetine during the first trimester had 1.5 – 2-fold increased risk for atrial and ventricular septal defects but another study found that the risk for cardiac malformation with paroxetine was within the expected cardiac malformation risk range for all pregnancies[3]. However, it is recommended to avoid its use during pregnancy except in those women who responded to it before pregnancy. Only one prospective study has found a possible association between cardiovascular anomalies and first trimester exposure to fluoxetine[23]. Therefore, monitoring the fetus with fetal echocardiography can help to detect any cardiac malformation in women on SSRI[3].

Another study found a significant association between sertraline and omphalocoele and between paroxetine and right ventricular outflow obstruction[24]. In December 2005, FDA issued a public health advisory about paroxetine use in pregnancy and paroxetine pregnancy category was changed from C to D[4]. Few case reports have reported withdrawal syndrome, functional bowel obstruction and urinary retention with the use of TCAs[3]. Behavioral abnormalities during the first 30 days of life after prenatal exposure to tricyclic antidepressants were reported in animal studies [25]. Exposure to TCA or fluoxetine either only during first trimester or throughout gestation, did not affect cognition, language or temperament in preschool or early school children[26, 27]. But a recent study has reported that the behavioral abnormalities are more frequent among premature infants born to mothers exposed to SSRI or venlafaxine[28]. However, the overall risk for birth defects is small with the use of SSRI compared to the risks associated with untreated depression and therefore they are still considered safe for use during pregnancy[3].

TREATMENT OF DEPRESSION DURING PREGNANCY

Decision to use antidepressants in pregnancy depends on the following factors[9]:

- Past history and severity of major depressive disorder before pregnancy
- History of perinatal depression during previous pregnancies
- Severity of present depressive episode during pregnancy
- Any suicidal tendencies or psychotic features

Based on evidence collected, the following strategies may be followed while treating depression in a woman of reproductive age group.

Before conception

- Treatment of depression in women of the reproductive age group can be started with an antidepressant that is safe for use even during pregnancy[9,29]
- Advice regarding birth control measures should be given while treating a woman in reproductive age group and to her partner, in case she is on an antidepressant which is relatively not safe in pregnancy[9]
- Any change in medication required should be done before pregnancy. This minimizes the number of exposures to the baby[9]
- Patient should be psychiatrically stable atleast three months before planning a pregnancy[9]

During pregnancy

- If the patient is suffering from mild depression, has responded well to medication and wishes to discontinue medications during pregnancy, she may be allowed to discontinue antidepressants. Such patients can be managed with cognitive behavioral therapy (CBT) or interpersonal behavioral therapy (IBT)[9] .
- Medications can be started for patients with mild depression for those who do not respond to CBT or IBT[1]
- Medication should not be discontinued in patients suffering from recurrent major depression as there is a high risk of relapse[9]
- It is better to continue with the same drug during pregnancy to which the patient responded well even before pregnancy[9]
- Monoamine oxidase inhibitors should be avoided as their safety during pregnancy is not known[25]. It is recommended that women on these drugs should be switched to alternative drugs preferably prior to conception or immediately upon diagnosis of pregnancy[30].
- The data regarding the use of bupropion, trazodone, venlafaxine, mirtazapine, nefazodone and escitalopram is inadequate. Hence, they should be avoided till adequate data is available[25].
- Fluoxetine and sertraline are usually considered safe for use since they are well tolerated and there is more data regarding their safety than the newer drugs[9,25,31]. Tricyclic antidepressants can also be used but side effects like orthostatic hypotension and constipation may be worsened during pregnancy. Among them desipramine and nortriptyline are preferred as they cause less hypotension and anticholinergic side effects[25].
- Patients may require a higher dose of the antidepressant during pregnancy due to enhanced metabolism, increased volume of distribution and induction of CYP 2D6 during pregnancy. Immediately after delivery the dose should be reduced to that used prior to pregnancy or 1/3rd the dose used during pregnancy[12].
- High resolution ultrasonography may be helpful to detect any congenital malformation at 18 – 20 weeks[32]
- Electroconvulsive therapy is preferred in pregnant women with suicidal intentions and psychosis[25]
- Supplementation of omega 3 unsaturated fatty acids may also benefit in depression because it has been suggested that a deficit of omega 3 unsaturated fatty acids may cause depression[33]
- It is important to discuss the safety and risks of antidepressants during pregnancy with the patient and her partner [9].
- Better to avoid the use of newer drugs as the information regarding them is not sufficient[9]
- Though previously it was suggested to withdraw antidepressants during third trimester to prevent perinatal problems there is a risk of worsening of depression during puerperium. Hence it is advised to continue them during third trimester. If discontinued they should be immediately re-introduced during postpartum[25].

During postpartum

- Postpartum blues are self limiting. No specific drug therapy is required. Support and reassurance is sufficient[25].
- IBT and CBT have been shown to be effective in reducing or eliminating mild depression. Especially those women who are uncomfortable with pharmacotherapy during lactation may be more comfortable with IBT or CBT[1,29].
- In case of severe depression during postpartum the same antidepressant as that used during pregnancy with the dose used prior to pregnancy can be used. For new onset of depression in postpartum half the recommended dose of the antidepressant should be initiated since women are highly sensitive to side effects after child birth. The dose can gradually be increased[34].
- Breast feeding should be advised. The baby would have already been exposed to the drug *in utero* in a higher concentration than that found in breast milk[9].
- Infants being breast fed by mothers on antidepressants should be monitored for irritability, sedation or any change in feeding patterns and especially if the neonate is premature or medically ill[4,35].
- Exposure to the infant can be minimized by breastfeeding before taking the daily dose of antidepressant and avoiding breastfeeding at the probable time of peak concentration of antidepressant in breast milk[4].

- Sertraline, paroxetine and nortriptyline are preferred for treating postpartum depression in a breast feeding mother as they yield undetectable levels in infant serum[36]
- It has been confirmed from recent studies that escitalopram is preferred over citalopram as its excretion in breast milk is lesser than the latter[37,38].
- Fluoxetine is usually not the first line medication option for postpartum depression as there are mixed reports regarding its adverse effects and also because of its long half life. But if a woman is already taking fluoxetine, monitoring the infant for adverse effects is advisable than switching antidepressants[39].
- Diphenhydramine is useful in women who have sleep disturbances during postpartum. Lorazepam may used in women having profound sleep disruption. Lorazepam is excreted in milk in very low concentration and has not showed any adverse effect in the infant[11].
- Use of transdermal estradiol has shown to benefit some women for postpartum depression. But whether it will have an effect on the hypercoagulable state of a woman during postpartum has yet to be studied[11].

CLINICAL TRIALS INVOLVING PREGNANT WOMEN

Since there is no conclusive evidence about the safety of antidepressant to be used in pregnancy there is a need for clinical trials in this area. But there is an ethical controversy whether pregnant women can be included in a placebo controlled study on antidepressants. A recent review based on literature search has summarized that it now ethically justified to include a pregnant woman if she agrees, in a randomized placebo controlled clinical trial of antidepressants. Such trials would help to find a suitable antidepressant which is efficacious and which will not cause any major harm to the pregnant woman, fetus or the neonate. They also will provide an evidence for making judgments about the risk-benefit ratio of antidepressant therapy which will help in individualizing therapy. Hence a well-conducted and ethically justified trial of antidepressants can improve the quality of care provided to a depressed pregnant woman[40].

CONCLUSION

Treatment of depression during pregnancy is a complex clinical situation. Moreover selection of an appropriate antidepressant is even more challenging. From the evidence available to date, risks of untreated maternal depression are more than the risks of serious adverse effects from antidepressant medication[41]. Treating a depressed pregnant woman requires a team approach on the part of the psychiatrist and obstetrician.

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Original Article

The Value of Single Complement Testing in SLE

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ABSTRACT

Objectives: Complement proteins are important in humoral immunity. In the hospital setting, complement component 3 (C3) and 4 (C4) are requested to determine the etiology of certain illnesses in addition to monitoring disease activity, particularly systemic lupus erythematosus (SLE). The aim of this study was to evaluate the correlation between C3 and C4, and to evaluate the significance of ordering both tests in patients with SLE during follow up.
Design: Retrospective review
Setting: King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia
Subjects: Complement levels were evaluated over a six month period (January 1, 2009 - June 30, 2009). Patient's sera were classified into three groups: Group I with SLE, Group II with rheumatoid arthritis (RA) and Group III with other rheumatological and non-rheumatological disorders.
Intervention: Serum level test
Main Outcome Measure: The correlation between C3 and C4
Results: One hundred and one (101) blood requests for C3 and C4 were evaluated. C4 hypocomplementemia was detected in 47/60 patients (78.3%), 9/16 patients (56.3%) and 1/25 patient (4.4 %) in Groups I, II and III respectively. This was in contrast to C3 hypocomplementemia which was detected in 21/60 patients (35%), 3/16 patients (18.8%) and 1/25 patient (4%) in Groups I, II and III respectively. There was a simple linear regression between C3 and C4 level ($p < 0.001$).
Conclusion: C4 hypocomplementemia is more frequently found than C3 hypocomplementemia in SLE patients. A correlation exists between the two tests, suggesting the adequacy of ordering a single test (C4) for the purpose of cost effectiveness.

KEYWORDS: autoimmune diseases, complement, systemic lupus erythematosus.

INTRODUCTION

Complement system is an important mediator of both natural and acquired immunity. It consists of approximately 30 proteins known as components that circulate in the body in an inactive form and become activated by three pathways; classical, alternative and mannose-binding lectin pathways. All pathways deposit complement component protein 3 (C3) on the target, as it occupies a central position in the complement activation process and is an important regulatory step. They are essential for antibody production, thus defending the body against infection[1]. Classical complement pathway is activated by antibody–antigen complexes found on bacterial surfaces and it is important for the adaptive immune response, whereas the alternative and mannose-binding lectin pathways are activated directly by bacterial cell surface components and are important in relation to the innate immune response[2]. Failure to activate C3 is associated with recurrent pyogenic infections, while deficiency of any component of the classical pathway, C1, C2, and C4 is associated with autoimmune disorders[3]. Assays of complement levels particularly C3 and C4 in the serum are one of the standard tests used for monitoring of patients with autoimmune disorders such as SLE[4].

Guidelines in clinical and laboratory immunology recommend that patients with SLE are monitored serologically every 6-12 weeks during the active phase and 6-12 monthly during remission, with multiple tests including C3 and C4[5-7] as disease relapse with certain end organ involvement can be determined by a decrease in the complement levels[8-10] .

The aim of this study was to determine the correlation between serum C3 and C4 level in patients with SLE and other autoimmune disorders during

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follow-up at the rheumatology clinic and to evaluate the significance of ordering both tests at the same time.

MATERIAL AND METHODS

The study was conducted at a tertiary teaching center in the western region of Saudi Arabia, serving a multiethnic community. All requests for serum complements C3 and C4 were evaluated between January 1st 2009 and June 30th 2009.

Demographic information recorded at the time of the study included age, gender, nationality, and diagnosis. Patient diagnoses were classified into three groups : Group I - SLE, diagnosed according to the American College of Rheumatology classification criteria (ACR)[11], Group II - rheumatoid arthritis (RA) diagnosed according to the ACR classification criteria[12] and Group III which included other diseases in the form of rheumatological disorders: polymyositis, antiphospholipid antibody syndrome, mixed connective tissue disease (MCTD), CREST syndrome (calcinosis , Raynaud's syndrome , esophageal dysmotility, sclerodactyly, telangiectasia), all diagnosed by rheumatologists according to predefined criteria and finally, non-rheumatological disorders (malignancy, infections, sarcoidosis, autoimmune hepatitis...*etc).*

One hundred and twenty three (123) samples were obtained for both C3 and C4 tests over the period of January1st 2009 - June 30th 2009. Twenty two samples were excluded due to duplicated order, missing file or incomplete data, leaving a total of 101 sample sera to be evaluated.

After reviewing the patients charts, all sera were classified into the following three groups: Group I SLE patients 60 / 101 (59%), Group II RA patients 16/ 101(16%) and Group III patients with other diseases 25/101 patients (25%). The latter included 16 patients with rheumatological disorders and nine with non-rheumatological disorders. The rheumatological disorders included: MCTD (4 patients), two patients with CREST, two patients with dermatomyositis, two patients with antiphospholipid antibody syndrome, two patients with Sjogren's syndrome, two patients with vasculitis, one patient with adult onset Stills disease and one patient with scleroderma. Patients with non-rheumatological disorders consisted of chronic inflammatory demyelinating polyneuropathy (2 patients), lymphoma (1 patient), tuberculosis (1 patient) and non-specific joint pain (5 patients).

C3 and C4 assays

The serum levels of complement proteins C3 and C4 were evaluated by nephelometry (antiserum to human complement factor C3 and C4; BN II; Dade Behring, Marburg, Germany). The normal reference range used by the clinical immunology lab at KAUH were: C3 between (0.75 - 1.65 mg/l) and C4 between (0.2 - 0.6 mg/l). Hypocomplementemia was defined as a level below the lower normal value (in case of C3 < 0.75mg/l and C4 < 0.2mg/dl.

This study was approved by the hospital ethical committee.

Statistical analysis

Statistical analysis was done using SPSS package (Statistical Package of Social Science - Version 10). The qualitative data was presented in the form of numbers and percentages. Chi-square with Yates correction was used as test of significance for qualitative data. The qualitative data were parametric and analyzed using Kolmogrov - Smirnov test. The quantitative data were presented in the form of mean and standard deviation (mean ± SD). One way Anova (t- test) was used for comparison of the three groups. Student's t-test was used for comparison of two groups. Significance was considered when p-value < 0.05. Pearson correlation, followed by simple linear regression was done to determine the type and degree of association between C3 and C4.

RESULTS

The mean age for the patients ± SD in years, Group I: 28.38 ± 11.75 (15 – 56), Group II: 45.06 ± 9.87 (26 – 67), and Group III: 33.3 ± 14.03 (15-73), p < 0.001. Female gender was predominant in 93/101(88 %) in the studied groups and Saudi nationals accounted for 58/101 (57.4 %) of the patients. Table 1 summarizes the demographic distribution of all studied groups. Using the one way Annova test, the mean age in RA group (Group - II) is significantly higher than SLE (Group - I) but lower than patients with other disorders (Group - III).

The mean levels of C3 were; in Group I: 0.91+ 0.41, in Group II: 1.08 + 0.33 and in Group III: 1.23 + 0.38 with a significant high difference between Group I and Group III (p = 0.002) and an insignificant high difference between Group I and Group II and (Group II and Group III). The mean levels of C4 were; in Group I: 0.167 + 0.12, in Group II: 0.25 + 0.21 and in Group III: 0.26+ 0.2 with significant high difference between Group I and Group III (p = 0.004)), and insignificant difference between Group I and Group II and Group II and Group III.

C3 hypocomplementemia was detected in 21/60 patients (35%), 3/16 patients (18.8%), 1/25 patient (4%) in Group I, II, and III respectively, with significant difference between all groups (p = 0.0088). Concerning C4 hypocomplementemia, it was detected in 47/60 patients (78.3%), 9/16 patients (56.3%) and 1/25 patient (4.4 %) in group I, II, III respectively with significant difference between all groups (p = 0.0062).

Table 1: Demographic distribution of the studied patients (n = 101)

Patient Characteristics	Group I SLE n = 60	Group II RA n = 16	Group III Others n = 25	Total (n) % n = 101	Test of Significance p-value
Age in years	28.38 ± 11.75	45.06 ± 9.87	33.30 ± 14.03	31.9 ± 14.03	0.001
Mean ± SD (range)	(15 - 56)	(26 - 67)	(15 - 73)	(15 - 73)	
Gender n (%)					
Male	4 (6.7)	1 (6.3)	3 (12)	8 (7.9)	0.63
Female	56 (93.3)	15 (93.3)	22 (88)	93 (92.1)	
Nationality n (%)					
Saudi	34 (56.7)	11 (68.8)	13 (52)	58 (57.4)	0.56
Non-Saudi	26 (43.3)	5 (31.3)	12 (48)	43 (42.6)	

SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis

Combined hypocomplementemia was detected in 23/101 patients only (in 19/ 60 patients in Group I (31.7%), 3 / 16 patients in Group II (18.8%) and only 1/25 patient (4%) in Group III, p = 0.019. Fig.1 represents the percentages of C3 and C4 hypocomplementemia in all the studied groups.

Isolated C3 hypocomplementemia (low C3 with normal C4) was detected in two patients only; Group I: 2 (3%) and zero in Group II and Group III which was statistically non-significant (p = 0.57). Isolated C4 hypocomplementemia (low C4 with normal C3) was found in 44 patients; Group I: 28/60 (47%), Group II: 6/16 (38%), and Group III; 10/25(40%). Once again it was statistically non-significant between all the studied groups (p = 0.73). Table 2 shows the distribution of C3 and C4 hypocomplementemia in the three studied groups.

As regards the clinical presentation in SLE patients with hypocomplementemia; low C3 was detected in 21/60 (35%), in which six patients (10%) had evidence of lupus nephritis (LN), C4 hypocomplementemia was detected in 47/60 patients (78.3%), in which nine (15%) patients had evidence of LN, while combined hypocomplementemia was detected in 19/60 patients (32%), in which six of them (10%) had LN.

By Pearson's correlation coefficient, there was a positive correlation between level C3 and C4 of the studied patients, which was statistically significant (r = 0 .43, p < 0.001, Fig. 2).

After detection of the above correlation, simple linear regression between the level of C4 and C3 was done. The level of C3 complement was dependent and the level of C4 was independent (*i.e.*, detection of C4 level enables us to estimate level of C4). By using the regression model from our patient's data, the following equation was obtained (p < 0.001).

C3 level = Constant + (B coefficient * C4)

The constant was (0.81) and the B coefficient (1.059)

C3 level = 0.81 + (1.059 * C4 level)

Regarding the C3 cut-off point, a value of < 1.165 will be helpful in prediction of SLE with sensitivity, specificity and validity of 72%, 58% and 71.7% respectively at a p-value of < 0.001. For the C4 cut-off point, a value of < 0.18 will be helpful in prediction of SLE flare with sensitivity and validity of 68.3% , 64% and 66.1% respectively at p-value = 0.006.

DISCUSSION

SLE is an autoimmune disorder in which the clinical manifestations are induced by deposition of antigen-antibody complexes in the tissues. Immune complexes can be detected only by tissue biopsy, but the pathological step of complement activation is

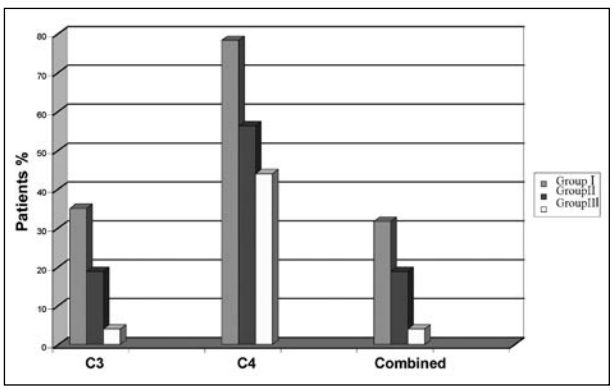

Fig. 1: Distribution of C3 and C4 hypocomplementemia in the three studied groups

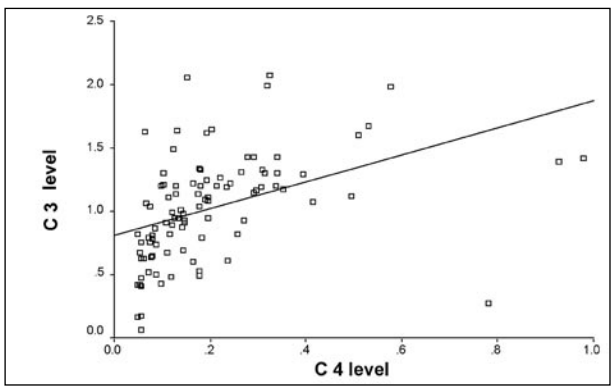

Fig. 2: Pearson's correlation coefficient showing a positive correlation between C3 and C4 level in the studied groups (r = 0.43, p < 0.001)

Table 2: C3 and C4 hypocomplementemia in all the studied groups

Type of Hypocomplementemia	Group I SLE n = 60	Group II RA n = 16	Group III Others n = 25	Test of Significance between two groups p-value#	Test of Significance between all groups p-value##
C3 N = 25 (%)	21 (35)	3 (18.8)	1 (4)	G1 = 0.21 G2 = 0.002** G3 = 0.12	0.0088*
C4 N = 67 (%)	47 (78.3)	9 (56.3)	11 (44)	G1 = 0.29 G2 = 0.004** G3 = 0.07	0.0062*
Combined (n = 23 (%)	19 (31.7)	3 (18.8)	1 (4)	G1 = 0.31 G2 =0.006** G3 = 0.15	0.019*

SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis
*Significant, ** Extremely Significant. #Least significant difference (LSD) test was used to compare between each two groups. ##One way Anova was used to compare between all groups.

evaluated by serum C3 and C4 measurement[13]. Initial reports have been conflicting regarding the importance of complement measurement in monitoring disease activity and assessing organ involvement as some support their usefulness[14] and others do not[15].

The mean age for the SLE patient was younger than the mean age for RA, which is expected as SLE is more predominant in a younger population[16]. The frequency of C4 hypocomplementemia in 67 /101 patients (66%) was higher than C3 hypocomplementemia in 25/101 patients (24.7%) in all the studied groups and was more frequent in SLE patients 47/60 (78.3%) than the RA patients 9/16 (56.3%) and patients with other diseases 11/25 (44%). This has been demonstrated previously in a study done in a western society of 550 serum samples taken from SLE patients, in which C4 hypocomplementemia was more frequent than C3 hypocomplementemia, regardless of the disease activity[17]. This could be explained by the fact that C4 level decreases before C3 and persists for longer periods in SLE[18].

Despite the fact that complement is not included in the classification criteria in the diagnosis of SLE, they have an important role not only in assessing disease activity, but in predicting prognosis as well. According to the literature, low complement levels, either isolated C3 or combined with C4 are associated with low survival in SLE patients due to recurrent infections[19, 20].

Another study was done in our society evaluating the mortality in 93 SLE patients; hypocomplementemia was detected in patients who died and patients that survived; C3 0.39 ± 0.13 versus 0.74 ± 0.05, and C4 0.07 ± 0.02 versus 0.14 ± 0.02[21].

A recent article reported in a study of 228 SLE patients with LN, blood tests in the form of C3, C4 and anti-dsDNA have a good negative predictive value, making the exacerbation of LN less likely[22].

RA is an inflammatory disorder with an elevation in the acute phase reactant. In our RA patients sera, none had an elevated C3 and only 1/16 (6.3%) had an elevated C4 level. This could be explained by controlled disease activity as the majority is in remission. This has been demonstrated in our population in which 34 out of 98 RA patients (35%) had the disease in its active form and 53 out of the 98 patients (54%) were receiving disease-modified antirheumatic medication (DMARDs)[23]. In addition, hypocomplementemia could be found in minority of RA patients (4%) with severe disease[24]. Our figure was similar for C3 and combined (3%) but was higher for C4 (9%) which could be explained by the possibility underlying combined RA and SLE that may have developed over time [24].

This research detected a strong correlation between both C3 and C4, which was statistically significant ($p < 0.001$). This has been demonstrated previously in another study by our group which concluded that 95% of C3 hypocomplementemia were significantly associated with C4 hypocomplementemia ($p < 0.001$)[25].

The total number of SLE patients in KAUH is high with more than 200 patients, each requiring at least four clinic visits per year and the request for many blood works including C3 and C4 representing a huge cost. According to our results, we may advocate ordering a single complement test. Due to the fact that C4 decreases before C3, we recommend ordering C4 and that C3 could be estimated by simple linear regression model: C3 level = 0.81 + (1.059 * C4 level). The only disadvantage is that the laboratory and health care personnel must be aware of the model. A major limitation of the study is the small sample size. We recommend doing a prospective multicenter trial, evaluating the complement level in SLE patients during remission and relapse.

CONCLUSION

Our study demonstrated three important results; there is a strong correlation between C3 and C4, C4

hypocomplementemia was more common in SLE patients than C3 hypocomplementemia, and finally the level of C3 hypocomplementemia could be predicted from the level of C4. Therefore, ordering a single test (C4) during follow up of SLE and RA patients would prove to be cost effective.

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Original Article

A Twelve-Year Experience in the Management of Calciphylaxis Resulting in Penile Gangrene

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ABSTRACT

Objective: To analyze the mode of presentation of patients with calciphylaxis induced penile gangrene and the outcome of management of the disease
Design: Prospective study (1998 - 2010)
Setting: Urology Unit, Mubarak Hospital, Kuwait
Subjects: Patients presenting with penile gangrene secondary to calciphylaxis were analyzed.
Intervention(s): Patients with moderate to severe penile gangrene had penile amputation
Main Outcome Measure(s): Etiological factors, mode of presentation, patient characteristics and the outcome of management
Results: Eleven patients were managed in the 12-year period. All patients (100%) had end stage renal failure (ESRF) and nine patients (81.8%) were on chronic dialysis at presentation. Poorly controlled diabetes mellitus was a co-morbidity in 10 patients (90.9%). Areas of gangrene were limited to the glans penis in nine patients (81.8%) and extending to the scrotum in two patients (19.2%). All patients had generalized calcified blood vessels on plain X-ray of the abdomen and pelvis. Eight patients (72.7%) required partial or total amputation of the penis. Three patients were successfully managed by debridement while one of them was too ill for surgical intervention. Seven patients (63.6%) were dead within three months of the diagnosis of penile gangrene.
Conclusion: Penile gangrene due to calciphylaxis is a rare disease seen mostly in patients with ESRF on chronic dialysis. Poorly controlled diabetes is a risk factor for the onset of penile gangrene. The disease has a high mortality in older patients with other co-morbid medical diseases. Immediate penile amputation may result in a satisfactory outcome in less than 50% of all patients.

KEYWORDS: chronic renal failure, penile amputation, calciphylaxis

INTRODUCTION

Calciphylaxis is a rare disease that develops in patients with chronic renal failure, hyperparathyroidism, and excessive intake of calcium/phosphorus regardless of the presence or absence of diabetes[1]. It is characterized by medial calcification and intimal fibrosis of medium and small arteries with secondary gangrene of the affected tissues[2].The disease process tends to spare the visceral vasculature. Unlike atherosclerotic disease, which affects all arteries and tends to cause luminal narrowing, systemic calciphylaxis is limited to the smaller arteries, arterioles and capillaries. The larger arteries responsible for palpable pulses are spared and patients usually have intact distal pulses[2].

Calciphylaxis is relatively common among women ranging from 40 to 60 years in age and has an incidence of 1 - 4% among patients with end-stage renal failure (ESRF)[3]. Penile calciphylaxis is rare; reported in 1 - 6% of patients with systemic calciphylaxis[4]. However, the disease may be under-reported and its incidence may be higher than appreciated[2]. The clinical presentation of calciphylaxis often begins as a mottling of the skin, with tender, painful violaceous lesions on the distal extremities, abdomen, buttocks, thighs, and breasts. Progression of the lesions may result in necrosis, gangrene, auto amputation, sepsis and death[5].

Plain film radiographs and computerized tomography (CT) often demonstrate severe calcification in the arteries and soft tissues. The diagnosis can usually be made from the clinical presentation and laboratory abnormalities of high calcium, phosphorous and parathormone (PTH) levels, and histological evaluation can confirm the lesion[2].

SUBJECTS AND METHODS

This prospective study included 11 patients who presented with penile gangrene secondary to calciphylaxis from 1998 to 2010. Data regarding

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Table 1: Profile of patients with penile gangrene

Patients	Age (years)	ESRF	Time of dialysis in years	Extra-genital lesions	Ca-P product (mg^2/dl^2)	DM	Management
1	56	+ve	2	-ve	77.4	Diabetic	Debridement
2	43	+ve	4	-ve	-	Diabetic	Partial penectomy
3	50	+ve	8	-ve	71.6	Diabetic	Partial penectomy
4	60	+ve	5	-ve	83.7	Diabetic	Total penectomy
5	70	+ve	12	+ve	81.7	Diabetic	Debridement
6	53	+ve	10	-ve	80.5	Non-diabetic	Partial penectomy
7	61	+ve	9	-ve	86.7	Diabetic	Partial penectomy
8	64	+ve	8	-ve	-	Diabetic	Partial penectomy
9	61	+ve	9	+ve	83.2	Diabetic	Total penectomy
10	65	+ve	5	-ve	79.5	Diabetic	Debridement
11	68	+ve	6	+ve	84.8	Diabetic	Partial penectomy

Penectomy = amputation of penis, ESRF= end stage renal failure, DM = diabetes mellitus

patients' age, associated ESRF and diabetes mellitus (DM), duration of dialysis, presenting lesions, serum calcium and phosphorus levels, radiological investigations, mode of treatment and its outcome were collected and analysed. All data were tabulated and analyzed using SPSS version 16.

This study was approved by the local ethical committee.

RESULTS

Penile calciphylaxis was diagnosed in 11 patients in the 12-year period under study. Table 1 and Fig. 1 show the characteristics of patients in this series. The mean age of the patients was 59.2 ± 8.08 years. All the patients had ESRF. At presentation, nine patients (81.8%) were on hemodialysis with a mean duration of hemodialysis of 7.6 ± 2.5 years. One patient had renal transplantation about three months before presenting with penile gangrene while one patient was in ESRF but not yet started on hemodialysis at the time of presentation with penile gangrene. Ten patients (90.9%) had diabetes mellitus. Serum calcium and phosphate were estimated in nine patients with a mean of 81.01 ± 4.5 mg^2/dl^2. Exragenital lesions involving the lower limbs, fingers or lower abdomen were seen in three patients (27.3%). All patients had evidence of vascular calcifications on plain X-ray study (Fig. 2). Management consisted of: local debridement and wound care in three patients (27.3%), partial penile amputation or partial penectomy in six patients (54.5%) and total penile amputation in two patients (18.2%). The technique we found effective for partial or total penile amputation involved raising ventral and dorsal penile skin flaps as shown in Fig. 3. In six patients where this technique was used, the wounds healed without any complications whereas in the other two patients where this technique was not used, wound dehiscence occurred. Seven out of eleven patients (63.6%) died within three months of the diagnosis of penile calciphylaxis. The disease had a favorable prognosis in a patient who had a kidney transplant before presentation, those patients with relatively short history of ESRF and hemodialysis, and the single patient who presented with penile gangrene

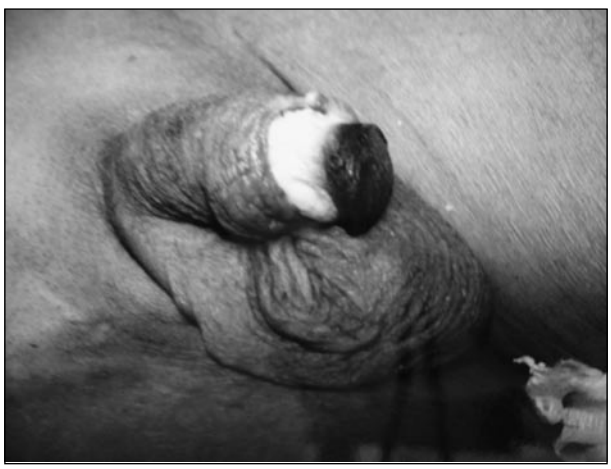

Fig. 1a: Extensive necrosis of glans penis and necrosis of shaft of the penis typical of penile gangrene. Patient is suitable for total penile amputation only.

Fig. 1b: Limited gangrene of the glans penis suitable for debridement or partial penile amputation

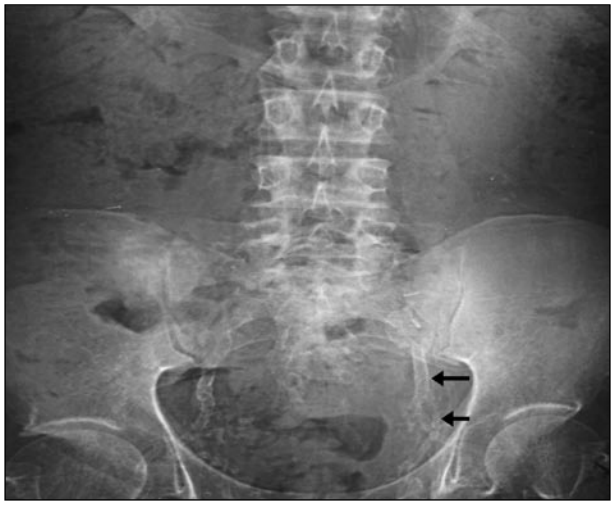

Fig. 2: Plain X-ray abdomen showing widespread calcified blood vessels typical of patients with calciphylaxis

but was not in ESRF. Hisopathological examination of the resected penises showed florid calcification of the blood vessels as shown in Fig. 4.

DISCUSSION

Calciphylaxis was first described by Selye *et al* in 1962 as a condition of calcium deposition in a hypersensitive environment in response to a challenging agent. They induced organ calcification in animals after they had been "sensitized" with one of several agents referred to as "calcifiers" (*e.g.*, dihydrocalciferol, vitamin D2, vitamin D3, and parathyroid hormone), followed by exposure to a "challenger" (*e.g.*, metallic salts such as iron and aluminum, egg albumin, or trauma)[6]. As reported previously and confirmed in this study, calciphylaxis is most often found in patients with chronic renal failure on long-term hemodialysis or peritoneal dialysis resulting in secondary hyperparathyroidism[7,8]. The elevated parathyroid hormone acts as a sensitizer in conjunction with elevated calcium, phosphorus levels and renal failure. After a latent period of unknown duration, triggering of calcium deposition occurs by challenging agents, such as corticosteroids, albumin infusion, iron overload from blood transfusion, calcium heparinate, immunosuppressive agents and vitamin D[9]. Although the exact interaction between the sensitizing and challenging agent is unknown, histologically calcific lesions are seen within the media of small and medium-sized dermal and subcutaneous blood vessels as shown in Fig. 4[7,10]. The penis has an extensive collateral blood supply protecting it from ischemic necrosis but in case of penile calciphylaxis the isolated penile gangrene is a focal manifestation of arterial calcification seen in calciphylaxis[11].

Most of the reported cases of penile calciphylaxis present around the fifth decade of life[1]. The mean age of our patients at presentation was 59.2 ± 8.08 years. Lal *et al* reported a mean age of 56 ± 12.9 years[6]. It has been observed that in patients with ESRF, a long period of hemodialysis usually preceeds the onset the disease. In our study of the 11 patients that presented with penile calciphylaxis, ten had long-term ESRF and period of hemodialysis (mean duration is 7.6 ± 2.5 years) with only one patient presenting shortly after a successful renal transplantation for reasons that were not clear at presentation and the disease was easily treated successfully by debridement only. In the study of Ohta *et al*, the mean time of hemodialysis was 40.9 ± 35.9 months[1] and in the study of Jhaveri *et al* the average time of hemodialysis was 55 months[9].

The relationship between diabetes mellitus and calciphylaxis has not been fully clarified, but the incidence of penile necrosis may be increased in diabetic patients with chronic renal failure[1]. The co-morbidity of diabetes mellitus in conjunction with systemic calciphylaxis may predispose to penile involvement because both diabetes mellitus and calciphylaxis appear to effect the same size vessels,

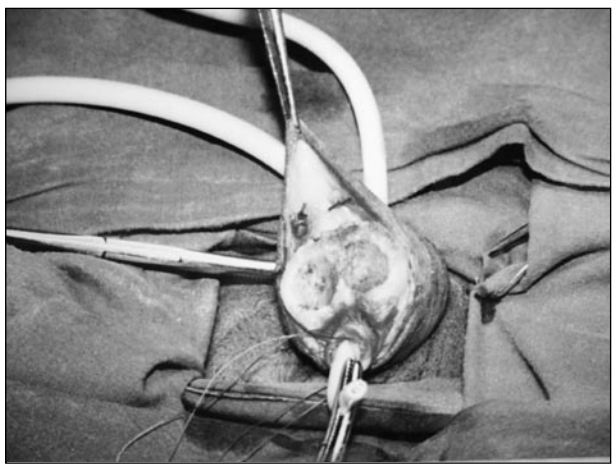

Fig. 3a: Technique of partial penile amputation. Note the dorsal and ventral penile skin flaps.

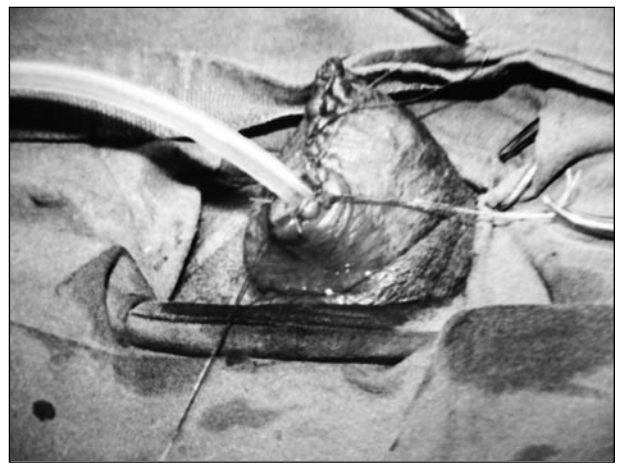

Fig. 3b: Final appearance after partial penile amputation

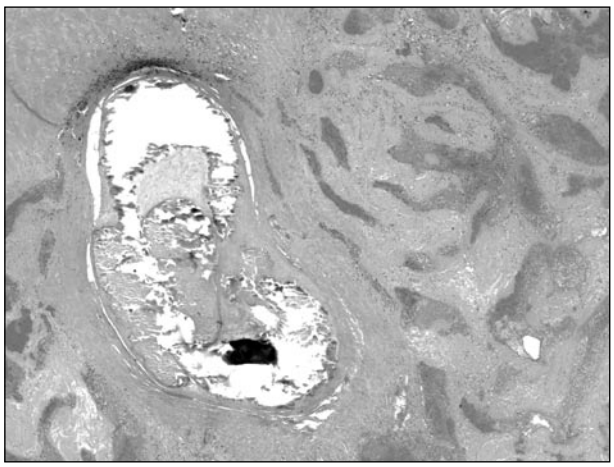

Fig. 4: Histopathological examination of resected penis showing florid calcification of the blood vessel

so an additive effect of both conditions may result in decreased perfusion of the penis, with subsequent necrosis[12]. In our study diabetes mellitus was present in 91% patients.

Karpman *et al* reported in their review that two-third of the patients with penile calciphylaxis had extragenital gangrene[2], whereas in our study extragenital lesions were observed in 22.2 %of patients.

Calcium metabolism is altered in patients with chronic renal failure. This alteration includes elevation of serum phosphate and decrease of serum calcium level, which causes secondary hyperparathyroidism. When the serum calcium - phosphate product exceeds 70 mg^2/dl^2, diffuse arterial and soft-tissue calcification occurs, which predominantly affects small arteries[13]. High serum phosphate level has been reported to promote the differentiation of vascular smooth muscle cells into osteoblasts[14]. In our study all cases had calcified blood vessels in the pelvis by plain X-ray. The calcium-phosphate product was reported only in nine patients and the mean was 81.01 ± 4.5 mg^2/dl^2. This is similar to the results obtained in the studies of Jacobsohn *et al* [12], who reported an average calcium-phosphate product of 81.5 mg^2/dl^2 and Jhaveri *et al*[9] who reported a mean of 84.44 mg^2/dl^2. In the study of Karpman *et al*[2], the mean calcium-phosphate product was 78.5 mg^2/dl^2 and it was less than 70 mg^2/dl^2 in two out of 33 patients diagnosed with penile calciphylaxis. Therefore, the diagnosis of calciphylaxis should not be excluded if the calcium-phosphate product is less than 70 mg^2/dl^2, especially, if clinical suspicion is high.

Treatment of penile calciphylaxis is controversial and varies from conservative management to surgical intervention in the form of subtotal parathyroidectomy and partial or total amputation of the penis[15]. Proponents of a conservative approach argue that aggressive surgery will not reduce morbidity and mortality because the underlying medical conditions are usually advanced and irreversible. Others suggest that if surgical therapy is not applied, super-infection and wet gangrene rather than mummification and auto-amputation will occur necessitating even more extensive surgery[16]. Conservative management includes measures that help in lowering calcium-phosphate product like phosphate binders, low phosphate diet, low molecular weight heparin and dialysis with solutions containing low phosphate and high calcium concentration[1,9,15]. Hyperbaric oxygen therapy has been reported to aid healing of the wounds in patients with penile gangrene[17].

Parathyroidectomy in patients with high PTH level appears to ameliorate clinical course of the disease. However, there is no strong evidence regarding improved survival[18,19]. Parathyroidectomy is indicated when progressive calcification develops despite medical therapy and it is best performed before extensive necrosis, gangrene and sepsis develop[15].

In our study, local debridement was performed in patients with poor performance status making them unfit for penile amputation. Control of local infection was easily achieved in three patients after penile amputation. In the patient with renal transplantation, the wound healed after local debridement and possibly due to the self-correction of any calcium-phosphate imbalance.

Jhaveri *et al*[9] recommended circumcision followed by debridement of the distal tip of the glans and in case of further necrosis of the distal penis, midshaft partial penectomy is performed. Jacobsohn *et al*[12] advised partial or total penectomy in all cases of identified penile calciphylaxis, as there are no preventive measures to avoid surgical intervention. However, there is no statistically significant difference in survival between patients treated with penile amputation and those treated with local debridement and wound care[2]. The other indications for penile amputation include severe pain and urinary obstruction[11].

The mortality rate in patients with penile calciphylaxis with ESRF is high despite aggressive management due to severity of associated systemic illness[15]. In our study, seven patients (63.6%) were dead within three months of the diagnosis of penile calciphylaxis despite intensive surgical treatment and attempts at corrections of any biochemical imbalances. Two of the patients that died also had extragenital lesions. Patients with extragenital lesions have been reported previously as having poor overall prognosis, a finding confirmed in this study[2]. Our experience indicates that the onset of penile gangrene may be seen as the harbinger of death in these patients and the need to adopt an aggressive management strategy to improve the mortality rate cannot be overemphasized.

CONCLUSION

Penile gangrene due to calciphylaxis is a rare disease seen mostly in patients with ESRF on chronic dialysis. Poorly controlled diabetes is a risk factor for the onset of penile gangrene. The disease has a high mortality and immediate partial or total penile amputation may result in a satisfactory outcome in less than 50% of patients.

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Original Article

Evaluation of Vaccine Induced Immunity to Hepatitis B Virus among Health Care Workers in a University Hospital in Iran

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ABSTRACT

Objective: To evaluate the level of anti-HBs antibody among health care workers (HCWs) in a university hospital in Shahre-Kord, Iran, during 2008-2009
Design: Prospective study
Setting: Charmahal-Baktiari province, Iran
Subjects: Two hundred and fifty seven health care workers (HCWs) in a university hospital
Intervention: Enzyme linked immunosorbent assay (ELISA)
Main Outcome Measure: Seroprevalence of anti-HBsAg (IgG)

Results: 85.6% of the individuals were female. Regardless of gender, 21 of the 257 (8.2%) HCWs lacked immunity, 91 of 257 (35.4%) were partially immune, and 145 (56.4%) exhibited immunity against the virus. The post-vaccination period was five years, in 221 (86%) and more than five years in 36 of the 257 individuals studied (14%). There were more male non-responders (15%) than female (8%). There was a significant relationship between post-vaccination period and anti-HBsAg antibody titer ($p < 0.05$).
Conclusion: Based on our results, the post-vaccination period of immunity to this virus in HCW workers is five years.

KEYWORDS: antibody, hepatitis B surface antigen, vaccination

INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most important global public health problems. It is estimated that 350 million people worldwide (7%) are chronic HBV carriers and 600,000 die each year from HBV-related liver disease or hepatocellular carcinoma[1-2].

Exposure to blood and body fluids presents a major risk factor for the development of HBV infection. It is a well-established fact that in an unvaccinated individual, the risk of acquisition of HBV infection after a single exposure to HBV infected blood, or body fluids ranges from six to 30%. Therefore, health care workers (HCWs) are at high risk of HBV infection due to repeated exposure[2-4]. In addition, the lack of effective infection control activities linked with a higher prevalence of HBV in Iran and neighboring countries, further augment the risk of nosocomial transmission of HBV to HCWs. Since 1982, when the HBV vaccine became available there has been a reported decline in the incidence of HBV infection and associated morbidity and mortality[5-8]. Therefore, from 1997, CDC recommended that all HCWs should be vaccinated against HBV[9].

The success of the different prevention strategies of the virus is affected by its distinctive characteristics. Although a safe and effective HBV vaccine has been available for several decades, strategies targeting high-risk groups failed to sufficiently control hepatitis B disease mainly because of difficulties in identifying individuals at high-risk and in implementation of the program[10-11].

The immune response to the HBV vaccine is assessed by measuring antibody levels at 6 - 8 weeks following treatment with three doses of vaccine. Hepatitis B surface antigen (HBsAg) specific antibody levels greater than 100 mIU / ml is generally taken to be protective[12-13]. Factors associated with decreased immune response include, increasing age, smoking, obesity, gender and genetic factors. Previously published immunological studies on HCWs from various parts of the world, have reported a non-responder rate of 12 - 21% for the HBV vaccine[14-16].

HBV infection is a major health care issue in both, the community and nosocomial settings in

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Iran, and data assessing immune response in HCWs is available. The prevalence of HBV in general population is considered to be 3 - 4%[17]. Thus, the possibility of nosocomial transmission in a health care setting is considerable. The aim of this study was to evaluate the immune response to HBV among vaccinated health care personnel in a university hospital in a central city of Iran, Shahre-Kord.

SUBJECTS AND METHODS

Two hundred and fifty seven HCWs were enrolled in the study conducted during 2007 - 2008. Among them, 92 were physicians, 146 were nurses/technicians, and 19 were auxiliary workers. A questionnaire including age, sex, date of the first vaccination and suspected exposure to HBV was filled in by the HCWs. The HCWs were vaccinated with Recombivax HB vaccine type. Using ELISA (Mega, USA), the level of anti-HBsAg (IgG) was measured in these individuals. Based on the antibody level, the individuals were separated into immune (>100 IU/ml), partially immune (10 - 100 IU/ml), and non-immune (<10 IU/ml) groups. Using Chi-square tests, the data were analyzed and p-values < 0.05 were considered significant.

This study was approved by the hospital ethical committee.

RESULTS

All of the 257 HCWs had previously had a complete program of vaccination against HBV. 85.6% of the individuals were female. Regardless of gender, 21 of the 257 (8.2%) lacked immunity, 91 of 257 (35.4%) were partially immune, and 145 (56.4%) exhibited immunity against HBV. The post-vaccination period was five years in 221 (86%) and more than five years in 36 of the 257 individuals studied (14%). There were more male non-responders (15%) than female (8%).

There was a significant relationship ($p < 0.05$) between post-vaccination period and anti-HBsAg antibody titer. Out of the individuals with a post-vaccination period of five years or less, 65% had high levels of immunity, sufficient to provide complete immunity, 31.7% had an antibody response corresponding to partial immunity, and 2.7% were non-immune to HBV. The individuals with a post-vaccination period of greater than five years, 16.7% were immune, 41.65% partially immune, and 41.65% non-immune to HBV. There was also significant relationship ($p < 0.05$), between occupational background and HBV antibody titer; individuals with a background of less than ten years had a higher antibody titer. There was also, a significant relationship ($p < 0.05$) between age and HBV immunity with HCWs less than 30 years old having immunity to HBV.

DISCUSSION

This paper records local epidemiological data regarding the immune response to HBV vaccine in HCWs. In this study, 8.2% of HCWs were non-responders, with a serum level of < 10 IU/ml of HBsAb. Our findings are in agreement with epidemiologic data regarding the immune response to HBV vaccination published in recent years[18-19].

In this study, age and gender represented two variables. The percentage of non-responder males (15%) was more than that of the females (8%, $p < 0.05$). This finding is in concordance with some other reports indicating higher responses in females[15-20]. Smoking, muscular anatomy, and certain genetic factors have been reported as probable reasons for the decreased immune response in males[20].

The highest rate of immune response was observed in younger HCWs (< 30 years), but this declined with increasing age ($p < 0.05$). Support for our findings comes from reports from other groups of workers, in which inadequate levels of antibodies in relation to increasing age are documented. Low antibody levels were found in 2.8% of individuals younger than 30 years, rising to 42.1% for those older than 60 years ($p < 0.0001$) of age[16]. The observations favor the hypothesis that with increasing age, vaccination-derived seroprotective antibody formation gradually decreases.

In our study, there was significant relationship ($p < 0.05$) between the antibody level and post-vaccination period. The vast majority (96.7%) of individuals with a post-vaccination period of five or less than five years, had immunity to HBV, while, only 58.26% of individuals with a post-vaccination period of more than five years were immune to HBV.

This finding is similar to that reported by some of our colleagues from other regions in Iran. They showed that the level of anti-HBV antibody in vaccinated individuals decreased significantly with time post-vaccination[21-23]. We conclude that the appropriate time for renewal of the vaccine is five years. However, some reports from abroad have suggested that this time should be six to seven years[24-25]. While the reason of these differences is not known, they might be due to factors such as differences in the received doses of vaccine and / or genetic / immunological differences among individuals. We recommend that since non-responders remain susceptible to HBV infection, the post vaccination HBsAb level should be determined for all HCWs as an infection control measure.

CONCLUSION

Based on our results, the maximum period of post-vaccination immunity to HBV in HCWs is five years.

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Original Article

A Three-Year Mandatory Student Research Program in an Undergradute Medical Curriculum in Turkey

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ABSTRACT

Objective: To evaluate the seven-year experience of the mandatory undergraduate student research program of Marmara University School of Medicine , Turkey
Design: Retrospective
Setting: Marmara University School of Medicine, Turkey
Subjects: Undergraduate students (from Year I, II and III; n = 289), mentors (n = 54) and graduates (n = 30) were enrolled. They were all involved in a longitudinal, mandatory and interdisciplinary research program. Students conducted a project under the supervision of a mentor in small groups and every year they improved their research skills step-by-step around specific themes. Each year the program ended with the Marmara Student Congress (MaSCo), at which all projects were presented.
Interventions: Student feedback evaluation, pre-prepared questionnaire filled by mentors and telephonic interview of randomly selected graduates
Main Outcome Measures: Number of projects presented in medical congresses, published in medical journals and feedback from students, mentors and graduates
Results: Between the years 2002 - 2007, students presented 467 research projects in MaSCo. Out of a total of 205, 2nd and 3rd year projects, 10 were published in international journals (4.87%) and nine (4.39%) in Turkish journals; 51(24.8%) were presented in national and 22 (10.1%) were presented in international congresses. Chi square trend analysis showed that students' satisfaction in all items of research activity increased from first to the third year. Sixty-three percent of graduates found undergraduate research activity beneficial.
Conclusions: Research programs should be one of the components of undergraduate medical education. We recommend that such programs be mandatory to develop research skills step-by-step.

KEYWORDS: mentors, research activities, teaching methods

INTRODUCTION

According to the WFME (World Federation for Medical Education) document on Global Standards for Quality Improvement - Basic Medical Education, medical schools must teach the principles of scientific method and evidence-based medicine, including analytical and critical thinking. In order to achieve this target, the medical curriculum should include elements for training students in scientific thinking and research methods[1]. Research experience as a medical student is shown to be strongly associated with postgraduate research involvement[2,3]. Therefore, engaging medical students in health research early in their careers is a promising strategy for promoting health research in the long-term.

Reports in the literature indicate that research experience is beneficial for students to improve their skills in critical thinking, information literacy, critical appraisal of literature, writing a study protocol and research papers, analyzing data, working independently and evaluating strengths and weaknesses of scientific papers[4-8]. Thus, student research activities have the potential to influence medical student's essential role as a researcher, the number of presentations and publications made, and the culture of evidence based medicine[9,10].

Although several authors agree with the contention by Stimmel in 1976[11] that research is helpful for preparing medical students for the practice of medicine and creating future scientist physicians, there is still no consensus regarding the implementation of research education in the medical curriculum. In 2002 Parkes reported that few medical schools taught scientific research comprehensively[12].

In this article, we summarize seven years of experience with a three-year, mandatory and interdisciplinary undergraduate student research program that has a step-by-step approach (different

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themes that promote different research types and help to develop a scientific vision), concludes with a student congress, and is embedded in the first three years of medical curriculum. We evaluate the outcomes of this program by presenting feedback from students, mentors and graduates.

SUBJECTS AND METHODS

1) Program description

Program structure: The student research program of the Marmara School of Medicine (MSM) is a mandatory program in the first three years. Between the years, there are three main differences in the structure of the program based on the themes, the formation of the student groups and the research planning process. All of the student research in this program is achieved through group projects. Each research group usually consists of four students. In the first year student research groups are formed by class number, while in the second year they are allocated randomly.

The main theme of research projects in the 1st year is "Explore Your Universe". First year is an introductory year for the research activities: students get experience of the basics of forming a research question, data collection tools, data entry and presentation. Some of the titles of first year student projects in recent years are "knowledge of and attitudes to global warming", "popular culture and its effect on first year medical students", "use of technological tools among first year medical students".

Second year topics are collected under the "Health and Society: Descriptions and Inferences" theme. In the second year, students are expected to perform a cross-sectional and more structured research project. A volunteer tutor functioning as a research mentor is appointed to each group at random. Students explore health related issues in the community. They mostly go to high risk groups and visit schools, workplaces, rest homes and households. Some titles of second year research projects in recent years are "knowledge, attitudes and behavior of food factory workers towards healthy diets", "the functional status of the elderly living in rest homes", "dating violence among university students".

In the third year, the main theme is "The Patient and Disease: Explanations and Causality" and the research groups are constituted voluntarily. Each group chooses a mentor from the list of research mentors on a first come first served basis. Third year students mostly deal with a specific group of patients or a disease and get more experience in analytic research approaches. Some titles of recent third year research projects are "the relationship between breast cancer and autoimmune thyroid disease", "the effect of drama supported patient education for the prevention of diabetes in patients with prediabetes", "opinions of patients on the time of discharge after thyroid surgery". Student reports from all three years have been presented at the annual "Marmara Student Congress" (MaSCo) since 2001.

The research program is assessed and evaluated in several ways. Each student group gets a score based on their research reports (70%) and their mentors' rating (30%) of the students' performance. Each report is assessed by two independent raters using a scoring guide.

Supportive means: Throughout the three years the research group activities are supported by a range of lectures. There is an introductory research and computer skills course for 10 x 2 hours in the first year.

In the second year, students participate in a 20 hour research planning workshop in small groups over five consecutive weeks. During the workshop, students learn about forming a research question, survey methods, ethical issues, and preparing their research proposals. At the end of the workshop, each group presents their research proposal and their work is evaluated by course tutors as well as other students. Furthermore, the Human in Medicine course described elsewhere[13], which also takes place in the second year, supports the formation of a research question about the theme "health and society".

Students are provided "study time" in the curriculum to work on their projects and meet with their mentors. For instance second year students have 15 x 4 study hours per academic year dedicated to research activities, whereas in the third year, students have 8 x 4 study hours for the same purpose. In 2008, the total number of mentors for 2nd and 3rd year students was 51. First year student groups are mentored by a team of five mentors.

MaSCo: A student congress in medical curriculum: MaSCo creates an opportunity for students to interact with their friends and teachers regarding their projects, which are the culmination of many months of work. During the two day congress, students present their research as either a poster or oral presentation. All completed research projects are accepted for MaSCo without any selection process except the submission before the deadline. At the end of the Congress, awards are given for the best oral and poster presentations. A pre-constituted awards jury including students and faculty staff rates each presentation using a structured presentation evaluation form.

2) Routine program evaluation: Feedback from students

Gathering feedback from students is a routine element of the program. At the end of every year a standardized feedback form is given to students.

Table 1: Year-wise number of student projects presented at MaSCo

Year	Explore your universe (Year 1)	Health & community (year 2) and patients & diseases (year 3)		Total n
	Poster presentation n	Oral presentation n	Poster presentation n	
2002	11	18	19	48
2003	17	25	19	61
2004	23	31	37	91
2005	38	26	31	95
2006	22	36	19	77
2007	32	38	25	95
Total	143	174	150	467

In this form the program is evaluated under three categories (organization, methods and content) using a five-point Likert scale (very bad, bad, moderate, good, excellent).

3) Additional program evaluation methods: feedback from mentors and graduates

A mentor is any faculty member who acted as a guide to at least one student research group between 2002 and 2007. Out of 76 mentors 54 (71%) agreed to participate. Mentors were asked to fill in a questionnaire *via* e-mail. In the questionnaire we asked about the number of student research projects presented in national/international congresses, the number of student research papers published in national / international journals and the number of student research reports not published but considered as publishable by mentors. Additionally, we performed face to face interviews with the mentors who accepted to be interviewed (n = 22); in the interviews mentors were asked about their experience of the student research program and MaSCo, and their suggestions for the future. The interviews were not recorded, but the interviewer took notes during interview.

In addition, 15 randomly selected graduates from the 2005 and 15 graduates from 2006 were interviewed by telephone using a structured questionnaire in order to explore the graduates' use of the knowledge and skills gained from the research program.

RESULTS

Between 2002 and 2007, 467 student research projects were presented as posters or orally in the MaSCo. The distribution of oral and poster presentations for each class is given in Table 1.

Student feedback

Table 2 shows the student feedback for academic year 2006 - 2007. Chi square trend analysis shows that students' satisfaction with all items of research activity increased from the first year to the third year. In the first year 4% students rated meeting the students' expectation as excellent, while the rate was 13.3% in second year and 24.8% in third year. Likewise satisfaction regarding "relation to future profession" was 15.5%, 23.4% and 28.6% among first, second and third year students respectively. The same trend was observed for the "objectivity of assessment" and "mentorship".

Mentor feedback

The total number of year II and III student research projects between 2002 and 2007 was 324. Two hundred and five out of them (63.27%) were reviewed for research quality by structured questions posed to 54 mentors. According to the mentors, 19 projects were later published as articles in peer reviewed journals. Ten were in international (4.87%) and nine (4.39%) in national journals. A total

Table 2: Student feedback on research program from the academic year 2006-2007

Items of research	First year		Second year		Third year		p-value*
	Very bad n (%)	Excellent n (%)	Very bad n (%)	Excellent n (%)	Very bad n (%)	Excellent n (%)	
Meeting the student expectations	22 (30.1)	3 (4.1)	21 (18.6)	15 (13.3)	9 (8.6)	26 (24.8)	< 0.01
Relation to future professional life	11 (15.5)	11 (15.5)	13 (11.7)	26 (23.4)	8 (7.6)	31 (28.6)	0.01
Objectivity of assessment	14 (19.7)	7 (9.9)	15 (15.2)	15 (15.2)	11 (10.9)	22 (21.8)	0.01
Mentorship	10 (14.1)	5 (7.0)	12 (12.2)	17 (17.3)	5 (4.9)	28 (27.5)	< 0.01

*Chi-square for linear trend

Table 3: Mentor feedback on the student research program

Positive	Negative
• Success is there if the dynamics in the group work well • Students learn how knowledge of medicine is developed • Best research award of the congress increases motivation • Students learn the technical aspects of scientific research and they improve their interpretation skills • A good exercise for students to prepare for real life • Data collection and presentation skills are improved • Interactive and enjoyable process • This is an effort of training-up for researchers of future • This process helps to develop a closer relationship between a student and teachers • Students understand causal relationships better • Students improve their communication skills and also their self- confidence increases after this program.	• We should not expect too much from student research activities. This is just an exercise, a pre-research activity. • There is very little doing unless students are motivated • Students do not know what kind of effort is necessary at different stages of the research process • Participation of both students and teachers in oral presentation sessions is not satisfactory • Well, students work on really good chosen topics, but how far can we rely on the validity of their data? • Working in community burns out the students. • Would it not be better to select more paramedical subjects? • Research needs protected time. It would be better to spare some structured time for both students and teachers. • Students should be better guided when they are selecting their research mentors

of 73 student research projects were presented in congresses, Fifty-one (24.8%) were in national and 22 (10.1%) in international medical congresses. Out of the evaluated 205 student projects, 29 (14.4%) unpublished projects were regarded as publishable in peer reviewed journals by mentors.

Mentors' open-ended feedback regarding their student research counseling experience is summarized in Table 3. According to the mentors, the program is beneficial to students as a means of preparing for professional life, improving presentation and communication skills, increasing self-confidence, understanding causal relationships and for the development of scientific knowledge.

Graduate student phone interviews

In telephone interviews with graduates the main topics discussed were the skills they developed during the research program and their use in their current careers, namely, SPSS statistical package program skills, literature search, data gathering and analysis, poster or oral presentation preparation, statistics and writing a scientific paper. Employed graduates (n = 14) used the skills and knowledge gained during undergraduate research activity at twice the rate of unemployed graduates (n = 16). The percentage of graduates who found undergraduate research activity "necessary" was 63.4%. Half of the graduates (n = 15) used skills and knowledge they learned during undergraduate research program. One third of the graduates (n = 5) took part in postgraduate research activities.

DISCUSSION

To best of our knowledge, student research program at the MSM is the first mandatory student research activity which takes a spiral approach (with different themes and a developing scientific vision) in the first three years of an undergraduate medical education. It is also the first in Turkey that includes a final student congress embedded into the curriculum. Our student research program could be considered as an effective scholarly activity with its 35% presentation ratio in scientific congresses of various disciplines, 9% publication ratio in peer-reviewed journals and another 14% considered as publishable by mentors. As an indicator of the process quality of this learning experience, students' satisfaction increased significantly in consecutive years. The great potential of medical students in medical research has been mentioned by several authors[12,14]. A study from Finland reported that 31% of medical students had an extracurricular research experience[15]. Cursiefen *et al* reported that students were involved in 28% of the Medline-indexed papers published by their faculty members during 1993 - 95[14]. All these results show that student research has a capacity to contribute to overall scientific enterprise with published articles in peer-reviewed medical journals. This capacity is especially important for increasing the number doctor-scientists, a number which has been in decline in previous decades[16].

A spiral pathway to encourage students using high-quality learning activities

There are several aspects of our program which address the high-quality learning activities mentioned by Vermunt[17]: use of knowledge, self-regulation of learning content, co-operative learning and deep processing of knowledge. In our program, students are provided with opportunities to use the theoretical knowledge that they acquire during the supportive lectures or workshops by concretizing and applying this knowledge in practice. As they work in teams they learn in co-operation with fellow students and share the tasks of learning. They also use deep processing strategies such as relating, structuring and critical processing while they are analyzing and interpreting their data.

It was reported that among the students' perceptions of factors influencing their decision to pursue a medical research career, perceived job satisfaction of mentors and prior research experience were significant factors[4]. Good mentorship provides a role model of a doctor-scientist and is a vital component of effective student research[18]. Out of our students 46% in the 2nd year and 58% in the 3rd year rated guidance of their mentor as satisfactory. This difference might be due to the difference of mentor determination between these two years. 3rd year students select their own mentors, whereas mentors are appointed by program co-ordinators in the 2nd year.

Furthermore, recognizing the best research projects at the end of MaSCo through the best oral and poster presentation awards has a positive impact on student motivation (the competitive environment directs students to perform at their best)[19]. Honoring best research was also reported as a motivating factor by our mentors. Another important contribution of MaSCo mentioned by our mentors was improvement in the students' communication and presentation skills. The students, who are members of the awards jury, evaluate the presentation of their peers through a prepared, structured check-list. This process makes them familiar to the concept of "peer review". With all these positive features MaSCo is considered by mentors and graduate students alike to be a potential tool for developing a research culture among the physicians of tomorrow.

Models of student research activities: voluntary and mandatory

Two models of student research activity are possible: voluntary and mandatory. According to WFME, training students in scientific thinking and research methods should be a part of a basic medical education curriculum. To reach this aim, the use of elective research projects conducted by medical students is suggested[1]. Hren *et al* reported that attendance at a mandatory course on research methodology during 2nd year of medical school is related to a positive attitude towards science[20]. Houlden *et al* report on medical students perceptions of an undergraduate research elective[4]. According to their results, even students who choose not to pursue careers in medical research perceive benefits in a mandatory undergraduate research elective such as the development of critical appraisal, information literacy, critical thinking skills and the opportunity to select an area of and form contacts for postgraduate training[4]. All these results are consistent with our own findings. According to mentors, our program is beneficial for students as a means of preparing for professional life, improving presentation and communication skills, increasing self-confidence, understanding causal relationships and developing scientific knowledge.

Early exposure to medical research

Our program gives opportunities to students to learn and experience medical research in the early years of medical school. Remes *et al* assessed medical students' research activity and found that 65% of the students, who had participated in research, had started their research during the first two years of medical school[15]. Gibson reported the same findings among dental students[21]. It is possible that students, who are keen on research and have an affinity for an academic career, start their scientific agenda at a very early stage of their undergraduate education. Among the clinical residents, it is also reported that academic interest declines during vocational training[22]. It seems to be crucial to start research education in the early years of medical school in order to keep students interest on scientific research and promote the doctor-scientist role as an option for the future.

Study limitations

Our study has several limitations. There is no comparison group to enable the attribution of positive findings only on our research program and the number of graduates interviewed is small and based on non-representative samples. This last factor makes it impossible to generalize the additive value of the research experience on the future careers of our graduates. Additionally, the cross-sectional nature of this study does not allow us to monitor changes in knowledge, attitude and skills regarding scientific research during different years of medical school.

CONCLUSION

A research program should be one of the components of undergraduate medical education. Engaging medical students in health research early in their careers increases their awareness of the researcher role of a medical student. Based on our encouraging experience we recommend this program to be mandatory to develop research skills in a step-by-step manner.

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Original Article

Learning Approches and Factors Affecting the Performance of Third Year Medical Students

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ABSTRACT

Objectives: To assess different learning approaches of 3rd year medical students of the College of Medicine, King Saud University (KSU) and to identify potential factors that may play a role in their performance
Design: Cross-sectional study
Setting: College of Medicine at KSU, Saudi Arabia
Subjects: Two hundred and fifty-six year-3 students
Main Outcome Measures: Learning methods, study materials used, prior preparation to the course and pattern of attendance at lectures and clinical sessions, exploring the relationship of these measures with medicine course mid-term written exam scores.
Results: Out of 256 students, 143 males and 88 females were responders. Their learning methods were: understanding 93 (40.3%), memorizing 24 (10.4%), and both 114 (49.4%) students. The study material used by them for preparation of examination was: text books 25 (10.8%), handouts 99 (42.9%), and pocket books 107 (46.3%) students. The number of usual study hours correlated significantly with exam scores ($r = 0.81$, $p < 0.0001$). Students who attended all clinical sessions scored higher marks in written examination. The multiple regression analysis identified the number of study hours, GPA, handouts as study materials, prior preparation to course, and number of clinical sessions absent as independent predictors for students' performance in the medicine examination.
Conclusions: This study has shown that, students' performance could be predicted based on their ways of learning and study materials used for preparing for their examinations. Validation of predictors in another sample is required so as to educate students with appropriate study strategies for better performances in their examinations.

KEYWORDS: education, medical exam, undergraduate

INTRODUCTION

Learning style and study methods are the process by which a student understands, retains and gains knowledge or skills to perform better in examinations. They are concerned with "how" learners learn, rather than "what" they learn. How students learn has always been a concern of teachers, educators and psychologists. Studies have shown that students learn in different ways and individuals tend to adopt distinct learning styles[1].

Studies suggest that learning styles are determined by personality traits as well as a variety of factors in the educational environment. Learning styles have significant relationship with outcome of the examinations, effectiveness in problem-solving and motivation for life-long or continuous education[1]. Knowledge of students' learning preferences and study approaches has important implications on the way the students should be taught and assessed in medical schools[1]. There are three other factors, including characteristics of teaching, the curriculum and the student that influence student learning. Each of these has an effect on the approach of learning adopted by students. The characteristics of teaching and curriculum produce a variety of learning environments or contexts, which result in students varying their approaches[2]. It is also reported that teaching characteristics influence different approaches to learning, including teaching methods, teacher enthusiasm and commitment and the level at which the information is presented[3].

Many researchers have described different factors that may play a role in the encouragement of surface approach to learning. These include overload of work,

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student's perception of the relevance of the content, assessment processes, reward for reproduction of content, poor teaching, and poor student teacher relationship[3-8].

A number of studies have indicated that the medical curriculum influences learning styles and study strategies. In schools with traditional curricula, students tend to adopt surface approach while in schools with problem-based curricula the students usually follow a deep approach. It was also observed that in schools with traditional curricula, the learning styles of students remained unchanged or shifted toward reproducing orientation. In contrast, in schools with problem-based curricula, the shift was toward meaning orientation[9-11]. A consistent correlation between poor performances of medical students using surface approach has been observed. Usually, such students express difficulties with courses they are studying. The frequently reported reasons for poor performance in the literature are difficulty in organizing study time effectively, feeling of being overloaded with vast study material, decreased motivation, difficulty in seeing the relevance of some subjects, difficulty in recalling previously acquired knowledge, and difficulty in applying acquired knowledge to practical situations[12]. Hence, some researchers have stressed on the need for understanding the phenomenon of learning by examining the student's experiences[13]. The present study was motivated by this concern. The College of Medicine, King Saud University (KSU) is one of the oldest medical colleges in the region, which follows traditional curriculum of teaching with two semester pattern and an intake of about 200 - 300 students each year. After two years of basic sciences (where most students memorize their subjects), when students are exposed to general medicine and general surgery courses for the first time in their 3rd year, they experience a lot of anxiety and stress as a result of their learning approaches and this could be changed. The objective of this study was to assess different learning approaches of 3rd year medical students of College of Medicine, KSU and to identify the potential factors that may play a role in their performance at the medicine mid-term written examination.

SUBJECTS AND METHODS

This study was carried out at the College of Medicine, KSU in March, 2009. An approval from the institutional ethical review board was sought prior to embarking on this study. The study subjects were, the 3rd year male and female students, who had completed their mid-term medicine written examination, after the 1st semester. Mid-term examination consists of 50 single best answer and context-rich multiple choice questions with reliability of 0.84, mean test score of 69.4%, and mean discrimination of 0.2521. The exam had good content-validity, as it was prepared using a blue print and results follow a fixed criteria reference of 60% marks as per university rules. Seventy percent of the questions were from higher order of Bloom's Toxonomy (*i.e.*, from application upwards to evaluation) and about 30% were of recall and comprehensive level according to examination guidelines.

A pretested and standardized close ended structured questionnaire was developed in adobe acrobat format and sent to the e-mail address of 256 students. The items in the questionnaire related to socio-demographic characteristics, parent's educational status, family members in the medical field, summer preparation of the medicine course, number of hours spent daily for studies, number of hours spent for exam preparation, learning style, study materials used, types of text books used, exposure to outside clinical training, absence from the number of lectures, absence from clinics, reasons for absence, and scores in mid-term medicine written examination. Students' mid-term written exam scores and grade point average (GPA) scores were obtained from Students Affairs department. The completed questionnaires were sent back by the students within stipulated one week time period.

STATISTICAL ANALYSIS

The data was converted into an MS Excel format and analyzed using the SPSS PC+ version 16.0 statistical software. Students' mid-term scores in written exam were used as an outcome variable and its normality test was assessed. Descriptive statistics (mean, standard deviation and proportion) were used to describe the study and outcome variables. Bivariate analysis to observe the significance of study variables in relation to outcome variable was carried out using student's t-test for independent samples, one way analysis variance followed by Duncan's multiple range test, and Karl Pearson correlation coefficient. A multiple regression model was developed to identify the predictors for the continuous outcome variable. A p-value of < 0.05 was considered as statistically significant.

RESULTS

Out of 256 students, 231(90%) responded with complete data for all the questions. The gender distribution of respondents was 143 (61.9%) male and 88 (38.1%) female. The students whose family members were in the medical field were 69 (29.9%). There were 64 (27.7%) students who had summer preparation for the medicine course. The style of learning was understanding by 93 (40.3%), memorizing by 24 (10.4%) and both by 114 (49.4%) students. The main sources of study material for information were text

Table 1: Comparison of mean values of written exam scores and its correlation in relation to the study variables- Bivariate analysis

Study variables	Written exam scores Mean (± SD)	t-value	F-value	r-value	p-value
Gender					
Male	13.9 (2.8) *	0.78	-	-	0.44
Female	13.6 (2.6)				
Family member in medical field					
Yes	13.5 (2.5) *	1.16	-	-	0.25
No	13.9 (2.8)				
Summer preparation					
Yes	14.2 (2.8) *	1.25	-	-	0.21
No	13.7 (2.7)				
Reading materials used					
Text books	13.4 (2.6) **	-	6.03	-	0.003
Handouts	14.5 (2.9)				
Pocketbooks	13.2 (2.5)				
Learning styles					
Understanding	13.9 (2.6) **	-	0.11	-	0.89
Memorizing	13.9 (2.2)				
Both	13.7 (2.9)				
Extra curricular clinical training					
Out of curriculum under supervision	14.1 (2.8) **	-	3.3	-	0.03
Out of curriculum without supervision	14.4 (2.5)				
Only curriculum training	13.4 (2.8)				
Lectures absent					
Not absent	14.7 (3.2) **	-	3.4	-	0.035
1-5 absent	13.9 (2.7)				
> 5 absent	13.4 (2.6)				
Clinics absent					
Not absent	15.0 (2.4) **	-	8.5	-	< 0.0001
1-5 absent	13.9 (2.7)				
> = 3 absent	13.0 (2.7)				
GPA scores	-	-	-	0.39#	< 0.0001
Usual number of study hours	-	-	-	0.81#	< 0.0001
No. of hours during exams	-	-	-	0.04#	0.52

*Student's t-test for independent samples; ** One-way analysis of variance; # Kari-Pearson correlation coefficient

books for 25 (10.8%) students, handouts for 99 (42.9%) students, and pocket books for 107 (46.3%) students. Clinical training beyond the regular curriculum under supervision was experienced by 52 (22.5%) students, beyond curriculum clinical training without supervision was experienced by 71 (30.7%) students and only curriculum clinical training was experienced by 108 (46.8) students. Only 31 (13.4%) students were present at all the lectures of medicine during the semester, whereas 105 (45.5%) were absent from 1 - 5 lecture sessions and 95 (41.1%) were absent from > 5 lecture sessions. Regarding clinical sessions, 52 (22.5%) students attended all of them, 98 (42.2%) were absent in 1 - 2 sessions and 81 (35.1%) students were absent in more than three sessions. The usual mean (± SD) number of study hours spent by the students per day was 2.9 (1.8) and during examination period the mean was 10.1 (3.7) hours per day. The mean (± SD) score of the written exam was 13.8 (2.7) out of 20. The mean (± SD) GPA was 3.85 (0.58) out of 5.

Bivariate analysis

The mean of the outcome variables (mid-term written exam scores) were assessed against different independent variables using, t-test, f-test and correlation coefficient (Table 1). Although number of study hours immediately before the exam did not make a big effect on the outcome variable, during the course usual study hours appeared to be more important determinant of improved exam performance scores ($r = 0.81$, $p < 0.0001$). GPA was found to correlate with the outcome variable ($r = 0.39$, $p < 0.0001$). Students who had extra clinical training beyond the curriculum scored higher marks in their mid-term written exam than those who did not ($F = 3.3$, $p = 0.03$). Students who attended all the clinical sessions scored higher marks in written exam when compared to others ($F = 8.5$, $p < 0.0001$; $F = 5.5$, $p = 0.005$). Those students who prepared for the exam using their handouts scored higher marks than those who used other sources of reading material ($F = 6.0$, $p = 0.003$).

Multivariate analysis

Multiple linear regression models were developed to observe the significant predictors for written exam scores (Table 2) in mid-term medicine examination. Five variables were found to be important predictors

Table: 2: Multiple linear regression of written exam scores with other variables

Dependent Variable	Independent * Variables	Coefficients	t-value	p-value
Written exam scores	(constant)	7.71	9.3	< 0.0001
	Usual number of study hours,	0.74	17.7	< 0.0001
	Reading materials used (handouts)	0.14	3.8	< 0.0001
	GPA	0.12	2.9	0.004
	No. of clinics absent	-0.12	-3.0	0.003
	Summer preparation	0.10	2.6	0.009

*Non-significant variables in the model: gender, presence of family members in medical field, number of study hours during exams, learning styles, type of clinical training exposure and number of lectures absent

for the mid-term written exam scores. These were: usual number of study hours during the course ($\beta = 0.74$; $t = 17.7$; $p < 0.0001$), using handout as a source of reading to prepare for the exam ($\beta = 0.14$; $t = 3.8$; $p < 0.0001$), GPA ($\beta = 0.12$; $t = 2.9$; $p = 0.004$), pre-course summer preparation ($\beta = 0.10$; $t = 2.6$; $p = 0.009$) and number of missed clinical sessions ($\beta = -0.12$; $t = -3.0$; $p = 0.003$). While, the first four variables show positive linear relationship with the outcome, the fifth one shows negative linear relationship. The model indicates r2 a coefficient of determination of 0.69, which means that 69% of change in written exam scores is explained by the above five independent variables. To keep the stability of the model because of the small number of the participating subjects, other non-significant independent variables were excluded from the model.

DISCUSSION

In most of the courses of a medical school, considerable attention is given to the development of curricular content, the organization of the teaching and the conduct of assessments and examinations. Little attention has been paid to the impact of these activities on the way students learn. A concern for this aspect of the educational effort is necessary to help students learn in an effective and efficient manner. A qualitative study reported that factors such as "personal abilities", "attitude, beliefs and motivation", "effort and perseverance" and other supportive factors were critical for students to achieve higher GPA's in a medical school in Iran[14].

The findings of this study show a clear statistically significant linear relationship of a combination of variables with the performance of the students in their general medicine exam scores. For better exam performance, the findings suggest that students should spend more time studying on regular basis during the course, have pre-course summer preparation, have good handouts as reading material, and avoid missing clinical sessions. Unexpectedly, the results did not show a significant relationship between students learning styles and performance. A possible explanation is the use of subjective way to ascertain this variable, which may lead to some misclassification. Some of the studies that aim to describe learning styles used a standardized inventory such as ASSIST (Approaches and study skills Inventory for Students)[15], or Kolb Learning style inventory[16], which was used in our study. Our subjective question about learning styles has shown, that 24 (10.4%) students were memorizing, 93 (40.3%) were trying to understand the subject, and 114 (49.3%) were following both the memorizing and understanding approach. As our study subjects were in the 3rd year of the course, their learning styles were a combination of both surface and deep learning. This pattern might be due to the traditional style of teaching basic science subjects in our medical college in the first two academic years. A study has shown that the use of deep learning styles in the final year of medical school predicts better performance in the final examinations but the same measures at the time of selection for admission to medical school did not predict students' performance in their exams[17]. Another study reported that higher surface-learning scores correlated significantly with younger age at admission to medical school, as well as with higher GPA. There was a positive correlation between GPA and surface learning in a group of students with more than four years of premedical experience[18].

Summer preparation prior to the course (such as having clinical sessions under the supervision of a qualified person) is important. Our data shows that students who had summer preparation scored higher marks in their exam and its coefficient is negatively linearly related to the outcome. The multiple regression model of this study reveals that students who have used hand outs as their study materials (coefficient positively linearly related) were scoring higher marks than students who were using textbooks and pocket books as study materials. The reason for our students using handouts with more success was due to the use of faculty handouts as the main source of MCQs for the examination paper.

Our findings contradict with the two studies by Gurung[19,20] who looked at the undergraduate's use of different study aids other than text books, such as summary sections, and found no correlation with exam performance.

Absenteeism is significantly associated with poor academic performance. It has been reported that good attendance showed good results and those with poor attendance are at risk of poor performance during examinations in basic medical sciences[21]. Concurrent with modern education technology, our medical college still continues to employ a great proportion of didactic teaching in the curriculum. Well organized and carefully presented lectures provide an up-to-date view of the subject[22]. They are invaluable for imparting in-depth knowledge to the entire group of learners at the same time, thus saving time and resources. Since the entire class is exposed to the same teacher, uniformity of the teaching experience is ensured[22]. However, the learner must be physically present and mentally receptive for learning to occur. In our results, it was found that those students who are present at all the lectures and clinics scored significantly higher marks in their exam, when compared with the students who were absent from some of the lectures and clinical sessions. Absence from the clinics by the students was statistically significant and negatively linearly related to the scored marks in the medicine examination. These results are in concurrence with the findings of an earlier study by BinSaeed *et al*[23] which reported that class absenteeism significantly affects the GPA's of students.

CONCLUSIONS

In light of the wide variety of study approaches adopted by students of a medical school, our exploratory preliminary data has indicated an impact of some variables and their independent relationship with the outcome of an examination. The multivariate results of this study would help to convince the medical school planners, teachers and educators to not only educate, but also motivate students to adopt appropriate study strategies for more effective academic learning and performance. The limitations of this study were its sample size, use of subjective tool, and outcome related to only a general medicine course; hence the study lacks generalizability of its findings to other subjects. Future research needs to be conducted on a larger sample of students in a more prospective and systematic way. Furthermore, learning and its strategies across the medical degree curriculum occur over time. Therefore, time series analyses and models that allow for prediction of change over time could be a useful approach for a future research project.

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Original Article

Diagnostic Performance of the Post-Exercise Systolic Blood Pressure Response for the Detection of Severe Coronary Artery Disease

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ABSTRACT

Objective: Systolic blood pressure recovery (rSBP) immediately after exercise effectively predicts survival and co-morbidity in those with atherosclerotic heart disease. The aim of this study was to evaluate the diagnostic value of the rSBP index for detecting coronary artery disease (CAD) severity.
Design: Prospective cross-sectional study
Setting: Shafa Hospital, Kerman Province, Iran between March and August 2009
Subjects: Ninety-four consecutive adult patients who were candidates for evaluation of CAD
Interventions: Exercise stress testing and initial coronary angiography
Main Outcome Measures: The rSBP was calculated by dividing the SBP three minutes after exercise by the SBP at peak exercise.
Results: Subjects with a high ratio of SBPs at 3 min of recovery to peak exercise were more likely to have severe CAD, adjusting for age, gender and body mass index using multivariate logistic regression analysis. The sensitivity, specificity, positive predictive value and negative predictive value of abnormal rSBP for predicting severe CAD were 42.6%, 81.8%, 50.0% and 77.1%, respectively. According to the ROC curve analysis, the rSBP measurement was a good indicator of severe CAD with areas under the ROC curves 0.652 (95% CI: 0.524 – 0.780). The optimal cut-off value for rSBP for predicting severe CAD was identified at 0.78 yielding a sensitivity of 60.7% and a specificity of 65.2%.
Conclusion: Systolic blood pressure ratio at three minutes post-exercise is a good diagnostic marker for predicting severe CAD with a high specificity and a good discriminative power.

KEYWORDS: blood pressure, diagnosis, exercise test

INTRODUCTION

Exercise-induced changes of cardiovascular parameters are commonly used for detection of coronary artery disease (CAD) as well as stratification of its risk and severity[1]. One of these changes that can be an important sign for detecting CAD severity and its related adverse events is decrease in systolic blood pressure (SBP) and blood pressure recovery ratio that is even more sensitive and specific than exercise-induced angina or ST-segment depression[2,3]. Some previous studies could confirm the high sensitivity, specificity and accuracy of exercise-induced hypotension in comparison with an ST-segment depression on treadmill exercise testing[4]. In a study by Amon *et al* a SBP recovery ratio of 0.8 or greater was more useful and applicable than ST-segment elevation for detecting CAD[5]. They could identify higher quality of this index in comparison with ST-segment depression with sensitivity 90% and specificity 95%. Some other researchers have shown a strong association between the angiographic severity of CAD and an attenuated blood pressure recovery[6,7]. It has even been hypothesized that SBP recovery immediately after exercise has prognostic value that effectively predicts survival and also co-morbidity rate in those with atherosclerotic heart disease[8]. However, some aspects of the predictive power of this ratio have been already questioned. First, some recent studies did not confirm the high sensitivity of the criterion in a large number of patients who performed upright bicycle exercise. Acanfora *et al* showed that rSBP had a sensitivity of 30%, specificity of 83%, and accuracy of 51%[9]. Core *et al* also could not demonstrate the prognostic power of rSBP[10]. Furthermore, the usefulness of this ratio after

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Table 1: Baseline characteristics of men and women undergoing coronary angiography and exercise testing

Characteristics	Ratio ≤ 0.85 (n = 70)	Ratio > 0.85 (n = 24)	p-value
Male gender	41 (58.6)	14 (58.3)	0.984
Age (yr)	52.77 ± 8.64	53.79 ± 10.93	0.681
Body mass index (kg/m^2)	26.37 2.08	25.82 3.19	0.443
Angiography report:			
LAD involvement	26 (37.1)	14 (58.3)	0.070
LCX involvement	16 (22.9)	11 (45.8)	0.032
RCA involvement	12 (17.1)	11 (45.8)	0.005
Exercise test report			
Maximum heart rate	151.53 ± 16.15	150.63 ± 31.71	0.895
Resting heart rate	94.68 ± 17.96	93.19 ± 24.52	0.786
Heart rate recovery	3.81 ± 1.00	3.51 ± 0.85	0.161
Maximum blood pressure	163.86 ± 18.94	135.83 ± 20.13	<0.001
Resting blood pressure	120.71 ± 11.80	128.75 ± 17.27	0.013
METs value	8.86 ± 2.31	7.51 ± 1.99	0.008

Data are presented as mean ± SD or number (%)

treadmill exercise has been suggested only in some subgroups of patients such as in patients with single-vessel CAD[11], those with left ventricular hypertrophy[12] or in normal subjects[13]. Besides, some other workers did not demonstrate the greater value of rSBP over the classical criteria of myocardial ischemia[14,15]. Moreover, our review of literature revealed only one study by Tsuda *et al* who confirmed that rSBP increased with the number of diseased coronary arteries[16]. The present study was designed to evaluate the diagnostic value of the rSBP index for detecting and evaluating the presence and severity of CAD in a sample of Iranian CAD patients.

SUBJECTS AND METHODS

Our study enrolled 94 consecutive adult patients who were candidates for evaluation of CAD and referred to the Shafa hospital for a first exercise stress testing and initial coronary angiography between March and August 2009. Those with concomitant valvular heart disease, cardiomyopathy, previous myocardial infarction, history or clinical evidence of systemic hypertension, electrocardiographic signs of left or right ventricular hypertrophy or left bundle branch block were excluded from the study. All patients gave informed consent before testing and the study protocol was approved by the institutional review board of the Kerman University of Medical Sciences.

Coronary arteriography was performed by the Sones techniques by an angiographer who was unaware of the exercise test results. Any coronary disease was defined as > 50% diameter reduction in a proximal or middle coronary artery or major branch. Severe coronary disease was defined as: 1) > 50% diameter stenosis of the left main coronary artery; 2) three-vessel disease with > 70% diameter stenosis in each major coronary artery system; or 3) two-vessel disease with > 70% diameter stenosis of the proximal left anterior descending coronary artery[6].

Exercise testing of the patients was conducted according to the standard and modified Bruce protocol and evaluated by an experienced observer without knowledge of clinical or angiographic data. Resting SBP was measured in a seated position and in a quiet room, using the mercury-column sphygmomanometer after 10 minutes of rest to exclude subjects with systolic hypertension. SBP was also measured at intervals of one minute during exercise and at peak exercise as well as after exercise for three minutes. The rSBP was calculated by dividing the SBP three minutes after exercise by the SBP at peak exercise.

Values were presented as mean ± SD for quantitative variables and percentage for categorical variables. Differences for unpaired values between the groups were analyzed by t test or by the Mann-Whitney U test when appropriate. Discrete data were also compared using Chi-square test or Fisher's exact test if required. The decline in SBP during recovery was assessed by calculating the ratio of SBPs at 3 min of recovery to peak exercise: a value above the 75th percentile for the population (which corresponded to a ratio 0.85) was considered abnormal. Multivariate logistic regression analyses were used to assess the associations of recovery and exercise blood pressure variables to severity of angiographic coronary disease after adjusting for each other and for confounding effects of gender, age and body mass index. Odds ratios (ORs) and Cochran-Mantel Haenszel confidence intervals (CIs) were calculated relating abnormal recovery and exercise blood pressure values to the presence of any or severe angiographic coronary disease. Sensitivities, specificities and positive and negative predictive values were calculated using standard definitions. Discriminatory capacity for SBP recovery was also

Table 2: Multivariable model for assessing relationship between abnormal recovery blood pressure ratio and coronary artery disease

Variable	Multivariate p-value	Odds Ratio	95% Confidence Intervals	
Severe CAD *				
rSBP > 0.85	0.041	3.573	1.052	12.142
Female gender	0.010	5.262	1.478	18.728
Age	0.003	0.904	0.846	0.966
Body mass index	0.162	1.337	0.890	2.010
Any CAD †				
rSBP > 0.85	0.118	2.609	0.785	8.677
Female gender	0.005	4.515	1.588	12.836
Age	0.001	0.900	0.846	0.958
Body mass index	0.204	1.212	0.900	1.632

CAD: Coronary artery disease
* Hosmer - Lemeshow goodness of fit test, $\chi 2 = 17.598$, df = 8, p = 0.024
† Hosmer - Lemeshow goodness of fit test, $\chi 2 = 6.880$, df= 8, p = 0.550

analyzed using the calculation of the area under the receiver operating characteristic (ROC) curve (C statistic) presented with 95% confidence interval. A value of 0.5 indicated that the model was equivalent to pure chance and a value of 1 indicated perfect discrimination. Predictive power analysis was carried out using the STATA statistical package (version 8.0; College Station, TX, USA) and comparative analysis using SPSS (version 13.0, SPSS Inc., Chicago, IL, USA). All p-values were two-sided, with statistical significance defined by $p \leq 0.05$.

RESULTS

The median value for the ratio of rSBP at 3 min of recovery to peak exercise was 0.77 (25th to 75th percentiles, 0.74 to 0.85). As shown in Table 1, the patient population was divided into two groups according to the ratio of SBP at 3 min of recovery compared with SBP at peak exercise: ≤ 0.85 (n = 70) and > 0.85 (n = 24). The two groups were comparable in terms of sex ratio, age and body mass index. Subjects with a recovery ratio > 0.85 were more likely to have stenotic left circumflex and right coronary arteries and had higher resting systolic blood pressures as well as lower METs value.

Subjects with a high ratio of SBPs at 3 min of recovery to peak exercise were more likely to have severe CAD, but not any CAD after adjusting for age, gender and body mass index using multivariable logistic regression analysis (Table 2). The sensitivity, specificity, positive predictive value and negative predictive value of abnormal rSBP for predicting severe CAD were 42.6%, 81.8%, 50.0% and 77.1%, respectively.

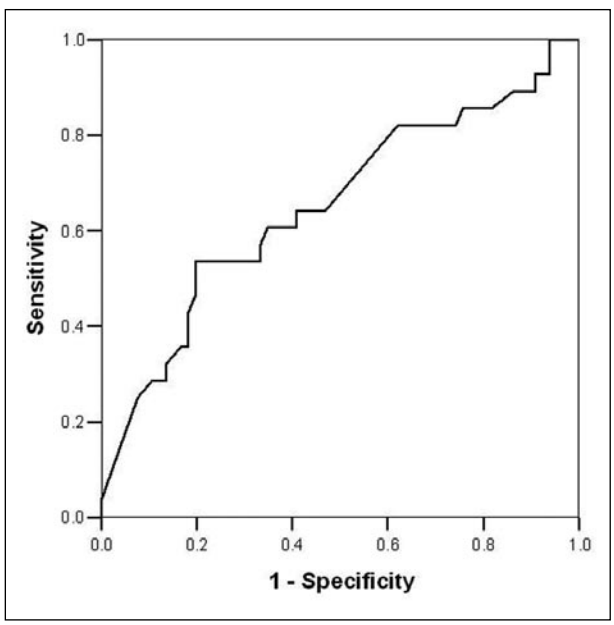

Fig. 1: The area under the receiver operating characteristic (ROC) curve for determining discriminatory capacity of SBP recovery for predicting severe coronary artery disease

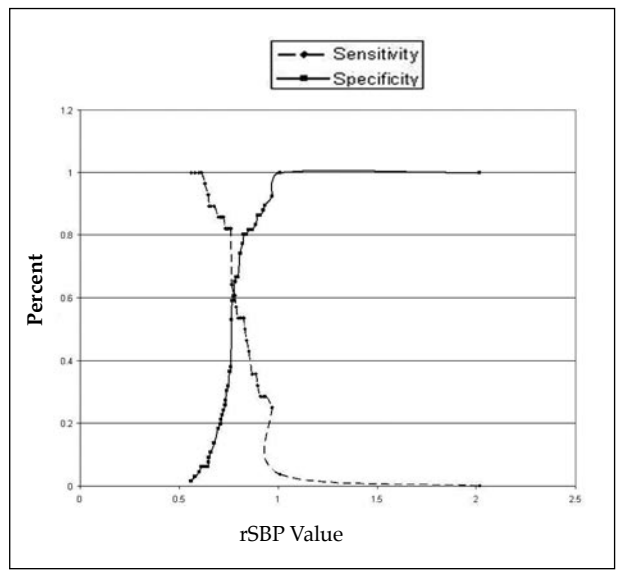

Fig. 2: Optimal cut-off point of rSBP for predicting severe coronary artery disease (0.775)

According to the ROC curve analysis, the rSBP measurement was a good indicator of severe CAD with areas under the ROC curves 0.652 (95% CI: 0.524 – 0.780) (Fig. 1). The optimal cut-off value for rSBP for predicting severe CAD was identified at 0.78 yielding a sensitivity of 60.7% and a specificity of 65.2% (Fig. 2).

DISCUSSION

In a population sample of adults referred for graded treadmill exercise testing and coronary angiography, a delayed decline in SBP after exercise as rSBP was independently predictive of severe CAD, even after adjusting for demographics and body mass index. Furthermore, regarding power of this index for predicting severe CAD, we obtained an acceptable specificity but low sensitivity for this parameter. Similar findings were obtained by other earlier and recent studies. In a study by Acanfora *et al* three minutes after exercise ended, rSBP was significantly higher in the CAD than in the normal coronary group with a sensitivity of 30% and specificity of 83%[9]. Also, McHam *et al* showed an association between a delayed decline in SBP during recovery and severe angiographic coronary disease with the sensitivity and specificity of 41% and 79%, respectively[6]. A delayed recovery of SBP has been also noted by others to be associated with angiographic severity of CAD[15-17]. In addition, Amon suggested that although the sensitivity of rSBP measure for detection of severe CAD was low, its specificity was quite high at about 80%. Thus, in terms of predictive power of rSBP value, this measurement is comparable with traditional ST-segment changes, and even has higher diagnostic performance over them. However, although rSBP has a positive correlation with the number of diseased coronary vessels, this correlation might not be to the extent of ST-segment changes.

Relationship between rSBP value and severity of CAD can be explained by some mechanisms. First, it has been demonstrated that blood pressure is mainly determined by a complex interplay between cardiac output, which is related to left ventricular systolic function and peripheral vascular resistance. Those with severe CAD develop left ventricular dysfunction during exercise. Immediately after exercise, there is rapid amelioration of left ventricular asynergy, resulting in an improvement in cardiac output. This would be expected to increase blood pressure, or slow down the decrease in blood pressure, after exercise[18]. Besides, peripheral vasoconstriction may also occur during exercise as a compensatory response to ischemic-induced left ventricular systolic dysfunction; this compensatory vasoconstriction may well persist during the first few minutes of recovery. The combination of a rapid improvement in left ventricular systolic function and increased levels of circulating catecholamines may well explain why patients with severe coronary disease have higher blood pressures during early recovery than those without disease[6]. Moreover, the exercise hypertension group exercised to a higher heart rate-systolic blood pressure product, representing greater myocardial oxygen demand. Thus, subjects with exercise hypertension had less severe angiographic coronary disease, with less severe ischemic limitation of myocardial work[7].

In the current study, the best cut-off point of rSBP measurement for diagnosing severe CAD was 0.78 yielding a sensitivity of 60.7% and a specificity of 65.2%. Abe *et al* indicated that a rSBP value of 0.86 was an appropriate cut-off point for distinguishing a patient with CAD from one with normal coronary arteries with the sensitivity, specificity, and accuracy of 79%, 83%, and 82%, respectively[12]. It seems that our cut-off point is lower than that demonstrated in previous studies[12,13]. Therefore, a lower cut-point yields higher sensitivity for discrimination of severe CAD from a normal coronary status.

CONCLUSION

Our study demonstrates that rSBP at three minutes post-exercise is a good diagnostic marker for predicting severe CAD with a high specificity and a good discriminative power. The best cut-off point of this index for discriminating severe CAD is 0.78 yielding a sensitivity of 60.7% and a specificity of 65.2%.

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Case Report

Pilomatrixoma: Features of a Case Diagnosed by Fine Needle Aspiration with Literature Review

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ABSTRACT

Pilomatrixoma (PMX) is a benign skin appendage tumor with differentiation toward hair cells, particularly hair matrix. It has classic histomorphology. However, fine needle aspiration cytology (FNAC) diagnosis may be extremely difficult and it can be mistaken for a malignant tumor. To our knowledge there are isolated case reports and some handful of series of cases reported in the literature elaborating cytologic features of PMX. We describe clinical and cytological findings in a 29-year-old male patient with skin nodule on the right upper arm. We also review the literature and conclude that identification of unique constellation of cytological features, *e.g.*, basaloid cells, ghost cells, refractile keratin material and foreign body giant cells *etc.*, in appropriate clinical context are most helpful in diagnosis and obviate unnecessary radical surgery.

KEY WORDS: cytology, fine needle aspiration, skin tumor

INTRODUCTION

Pilomatrixoma (PMX) is a benign skin appendage tumor of hair matrix cells and is also known as 'calcifying epithelioma of Malherbe'[1]. The term PMX is preferred since the former name may give the unwary clinician a false impression that the lesion is malignant. It commonly presents as a slow growing dermal or subcutaneous nodule. Since Woyke *et al*[2] first reported the cytology of six cases in 1982, a spectrum of cytological features of PMX have been described over the years[3-5]. However, it still poses a diagnostic challenge to cytopathologists as situations leading to mistaken diagnosis arise very often leading to therapeutic implications for the patient, especially when it is misinterpreted as malignant. We review the literature and report clinical and cytological findings in one such case of PMX which was correctly diagnosed by fine needle aspiration cytology (FNAC) pre-operatively.

CASE REPORT

Clinical findings: A 29-year-old male patient presented to the surgical out-patient department with a firm, tender subcutaneous nodule on the right upper arm. It was gradually increasing in size. It measured 2 x 2 cm at the time of presentation and showed slight discoloration of overlying skin. Systemic examination was unremarkable. Patient was referred for FNAC with a clinical diagnosis of soft tissue tumor.

Cytology: A grossly particulate aspirate was obtained using a 22 gauge needle attached to 10 ml plastic syringe. Both wet alcohol fixed and air dried smears were made. They were stained with Papanicolaou and Diff-Quick stains respectively. The smears were interpreted by the same cytopathologist who did the aspirate. They were highly cellular composed mainly of basaloid cells which were present as tightly arranged cell clusters of varying sizes as well as isolated cells (Fig. 1a). These cells had a high nuclear cytoplasmic ratio and scanty basophilic or pale cytoplasm. However, many of the cells lacked cytoplasm completely and were represented only by naked nuclei showing degenerative changes. Better-preserved cells showed small to medium-sized, round or oval nuclei with dispersed or slightly granular chromatin having prominent nucleoli in some of them. The nuclei were usually quite uniform, but occasionally moderate variation in shape and size, as well as some hyperchromasia could be observed. Some of the isolated basaloid cells showed smudging artifact similar to those that may be observed in aspirate from small cell carcinoma. A few cell clusters with squamous

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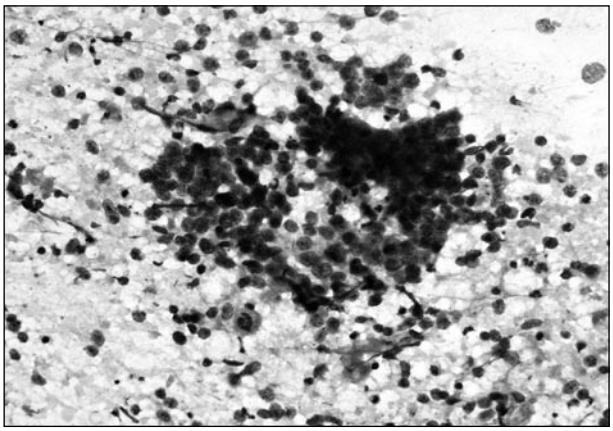

Fig. 1a: Highly cellular smears with tight clusters and discretely lying basaloid cells (Papanicolaou stain, X 200)

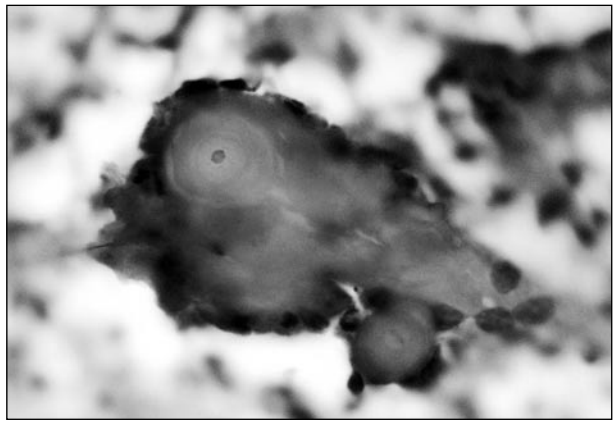

Fig. 1b: Sharply outlined clumps of refractile keratin material (Papanicolaou stain, X 1000)

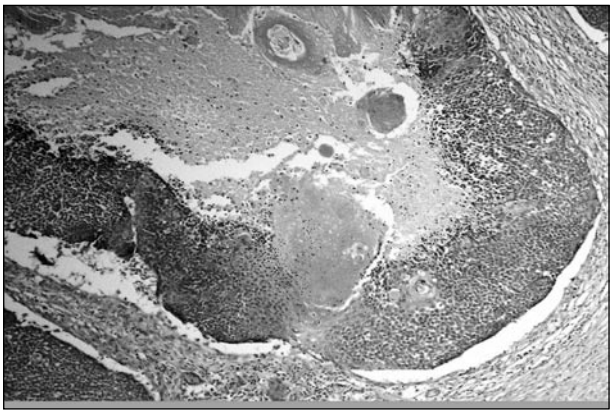

Fig. 2: Histologic section of pilomatrixoma showing islands of basaloid epithelial and ghost cells surrounded by stroma rich in inflammatory cells (H & E stain, X 200)

differentiation were also seen. Shadow or ghost cells (cells with distinct cell borders and characteristic central pale nuclear zone) were not observed. However, few small and sharply outlined clumps of keratin material were seen on Papanicolaou stain (Fig. 1b). Scattered multinucleated giant cells admixed with basaloid cells were noticed. Background displayed inflammatory cells including histiocytes, neutrophils and cell debris. There were no calcific deposits.

A cytological diagnosis of skin appendage tumor highly suggestive of PMX was rendered keeping in view the clinical presentation. The nodule was excised and histopathology confirmed the cytological diagnosis of PMX. Histology sections revealed a well defined lesion composed of islands of basaloid cells displaying abrupt transition into sheets of ghost cells along with scattered multinucleated giant cells and inflammatory cells in stroma (Fig. 2).

DISCUSSION

PMX is a benign skin appendageal tumor whose histogenesis and histology are well known. It usually presents as a firm, solitary dermal or subcutaneous nodule with normal overlying skin in children and young adults. The most common sites are head and neck area or upper extremities. It is rarely diagnosed clinically and like majority of cutaneous neoplasms punch or excision biopsy is the preferred method of diagnosis. However, FNAC can serve as a quick and accurate way to establish a pre-operative diagnosis.

The FNAC differential diagnosis of PMX includes benign mimics (*e.g.*, epidermal inclusion and trichilemmal cysts, adnexal tumors, granulomatous inflammation, giant cell lesions) and malignant neoplasms (*e.g.*, basal cell carcinoma, squamous cell carcinoma, small round cell tumors, malignant skin appendage tumors). Salivary gland lesions also enter in the differential diagnosis, especially if the lesion is located in the parotid or submandibular area[6].

A review of the English literature (Table 1) identified several cases of PMX misinterpreted cytologically. The major pitfall is the over interpretation as malignant. The causes of erroneous diagnoses include high cellular yield, presence of small primitive-appearing cells with increased nuclear-cytoplasmic ratio, prominent nucleoli, nuclear moulding, mitotic figures and a background rich in debris and inflammatory cells resembling tumor necrosis. The predominance of one of the cellular components (namely, the squamous cell or basal cell element) as well as the occasional lack of ghost cells and giant cells, may compound the diagnostic problem further.

Despite of the aforementioned difficulties, we believe that the benign nature of PMX can be recognized in FNA smears. Features that aid in the recognition of a benign lesion include a bland and evenly distributed chromatin pattern; regular nuclear contours in the small primitive uniform cell population; and lack of nuclear atypia in the squamous cells. Sanchez *et al*[3] recommended the importance of examining smears with Papanicolaou stain and Diff-Quick since the nuclei of basaloid cells may appear unduly enlarged in smears stained with Diff-Quick.

Table 1: Review of clinical features of cytologically discrepant PMX cases

Author	No of cases	Age, years (mean)	Sex	Location	Size (cm)	Clinical diagnosis	Initial cytologic diagnosis	Revised cytologic diagnosis	Histologic diagnosis
Thapliyal *et al*, 2008[7]	1	32	M	Arm	5 x 4	-	Small round cell tumor	-	PMX
Bhadani *et al*, 2007 [8]	5	8 - 32 (19)	F	Cheek (1) Neck (1) Arm (1) Preauricular (1) Shoulder (1)	2 - 5 (3.4)	Sebaceous cyst (1) Tuberculous lymphadenopathy (1) Dermatofibroma (1) Reactive lymphadenopathy (1) Lipoma (1)	PMX (3) Skin appendage tumor (1) Epidermal inclusion cyst / squamous cell carcinoma to be ruled out	-	PMX
Siddaraju *et al*, 2007[9]	1	-	-	Neck	-	Lymphadenitis	Metastatic carcinoma	-	PMX
Singh *et al*, 2007 [10]	1	1	M	Neck	1.5 x 1	-	Small round cell tumor, ? Rhabdomyosarcoma	-	PMX
Sivakumar, 2007 [11]	1	62	F	Submandibular	4.6 x 3.5	Suspicious for malignancy	Mucoepidermoid carcinoma/ squamus cell carcinoma/ calcifying odontogenic tumor	-	PMX
Lemos & Brauchle, 2004 [12]	1	10	F	Parotid region	3	-	Suspicious for carcinoma	-	PMX
Lemos *et al* 2001 [13]	9	12 - 70 (39)	5 F 4 M	Face (3) parotid (1) Neck (3) Arm (2)	0.7 - 2.5 (1.3)	-	PMX (2) ? squamous cell carcinoma (2) ? small cell carcinoma (2) Basal cell carcinoma/PMX (1) Skin adnexal tumor (1) Benign epithelial cyst (1)	PMX	PMX
Domanski and Domanski, 1997 [14]	9	8 months 63 (31)	6 F 3 M	Cheek (3) Neck (3) Arm (1) Parotid mass (1) Breast (1)	0.8 - 2.3 (1.4)	PMX (1) Dermoid cyst (3) Hemangioma (1) Lymph node (1) Adnexal tumor (1) Suspected carcinoma (1)	PMX (4) PMX vs benign adnexal tumor (1) Cyst (2) Adnexal tumor vs pleomorphic adenoma (1) Benign adnexal tumor (1)	-	PMX
Kumar and verma, 1996[15]	11	4 - 58 (18)	4 F 7 M	Neck (5) Chest wall (1) Upper arm (1) Forearm (1) Buttock (1) Cheek (1) Ear lobe (1)	-	Tuberculosis (5) Cysticercosis (2) Cyst (2) Soft tissue tumor (1) Metastatic carcinoma (1)	PMX (3) Benign skin appendage tumor (3) Giant cell lesion (1) Cyst (1) Insufficient (2) Squamous cell carcinoma vs epidermal cyst (1)	PMX (6) Not done (5)	PMX(5) Not available (6)
Sanchez *et al*, 1996[3]	9	4 - 51 (11)	7 F 2 M	Parotid mass (3) Neck (3) Cheek (1) Shoulder (1) Leg (1)	1 - 2.5 (1.5)	Parotid tumor (1) Lymph node (1) Not done (7)	PMX (5) Malignant small round cell tumor (1) Monomorphic adenoma (1) Pleomorphic adenoma (1) Insufficient material (1)	-	PMX
Wong *et al*, 1994 [16]	1	24	M	Neck	2	-	Squamous cell carcinoma	-	PMX
Kinsey and Coghill, 1993[17]	1	69	M	Neck	11 mm	-	Squmous cell carcinoma	-	PMX
Layfield and Glasgow, 1993[6]	3	-	-	-	-	-	PMX (2) Basal cell carcinoma (1)	-	PMX
Chan and McGuire, 1992 [18]	2	42	F M	Parotid mass	-	-	Pleomorphic adenoma	-	PMX

Table 1 Continued

Ma *et al*, 1991[19]	1	56	M	Neck	1	-	Malignant adnexal tumor vs metastatic squamous cell carcinoma	-	PMX
Bhalotra and Jayaram, 1990[20]	1	30	M	Left breast	4 x 3	-	Giant cell lesion	-	PMX
Gomez-Aracil *et al*, 1990[21]	4	19 - 40 (38)	2 F 2 M	Trapezius (1) Supracondylar (1) Forearm (2)	0.5-3 (1.5)	-	PMX (2) Suspicious of carcinoma (1) Carcinoma (1)	-	PMX
Chan and McGuire, 1989[22]	1	44	M	Parotid mass	2	-	Squamous cell carcinoma	-	PMX
Woyke *et al*, 1982[2]	6	8 - 73 (35)	-	Cheek (2) Eye lid (1) Temporal region (1) Arm (1) Thigh (1)	1.3-3	-	Malignancy (4) Descriptive (2)	-	PMX

M = male, F = Female, PMX = pilomatrixoma

The presence of ghost cells seems to be the key or pathognomonic feature. However, despite their abundance in histologic sections, their detection was reported to be difficult in cytologic smears and they may not be present at all as in our case. This is probably due to difficulty in detaching these cells during aspiration. Woyke *et al*[2] reported the presence of ghost cells in only three out of six cases, while in a series of three cases by Solanki *et al*[23], they were not easily visualized. Gomez-Aracil *et al*[21] noted the ghost cells in Giemsa-stained smears from all four cases, but these cells were not visible in Papanicolaou-stained smears. In the case reported by Ma *et al*[19], ghost cells were not present in the first FNA smears but were easily recognized after repeat aspiration.

Wong *et al*[16] reported an important feature which, if present, helps in establishing the cytologic diagnosis of PMX and should alert the observer to search for the more diagnostic features. This is the presence of sharply outlined masses of refractile keratin clumps, which they interpreted as sheets of ghost cells. This feature is recognized mainly in the Papanicolaou stain smears. This has been mentioned briefly in previous reports but was underemphasized. It was described by Woyke *et al*[2] as eosinophilic clumps, and by Chan and McGuire[18] as birefringent keratin material.

CONCLUSION

In conclusion, a diagnosis of PMX should be considered in the differential diagnosis of small cell and keratinizing lesions of the skin, and it is possible to render an accurate diagnosis based on FNA smears after careful analysis of all cytologic features in the light of clinical information.

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Case Report

Anthracotic Mediastinal Lymphadenopathy: Case Report

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ABSTRACT

We report the case of a male patient, known to have rheumatic mitral valve disease, who presented to us with huge mediastinal lymphadenopathy and dry cough. He was a life-time non-smoker and the only past medical history was his exposure to smoke during the Gulf war in 1991. This patient was in Kuwait during the Iraqi invasion and had a continuous exposure to the polluted environment. Mediastinoscopic lymph node biopsy confirmed the diagnosis of anthracotic reactive lymphadenopathy and excluded other causes. Anthracotic pigmentation is a common finding in mediastinal lymph node biopsies especially in smokers, but symptomatic huge lymphadenopathy was rarely reported. This observation and its correlation to the gulf war are also not reported in the literature.

KEY WORDS: anthracosis, gulf war, mediastinal lymphadenopathy

INTRODUCTION

Anthracosis is a form of pneumoconiosis, which is usually caused by coal dust or by a smoky polluted environment. Anthracosis usually presents in pulmonary forms, but extrapulmonary forms such as lymphadenopathy, esophageal and hepatosplenic forms *etc*. are rarely reported[1,2]. In this report we present a case of anthracosis with hilar and mediastinal adenopathy. The etiology is postulated to be the exposure to smoke from the burning oil wells during Gulf war I.

CASE REPORT

A 43-year-old Indian male, an electrical worker for 20 years and a diagnosed case of rheumatic heart disease with mitral stenosis since many years was referred to the chest unit for evaluation of a persistent dry cough of two months duration. There was no associated fever, breathlessness, hemoptysis or chest pain. He was a life-time non-smoker and had no past history of any relevant occupational exposure. He gave no history of any relevant past respiratory symptoms or any pulmonary consultation before this visit. He was working in Kuwait since 1990. He gave history of exposure to heavy smoke due to burning of oil wells during the Gulf war in 1991.

Clinical examination revealed a healthy, middle aged male. There was no clubbing or generalized lymphadenopathy and vital signs were normal. There were clinical features of mitral stenosis, with no regurgitation or cardiac failure. Examination of respiratory system was unremarkable. There was no organomegaly and examination of nervous system was normal.

Routine hemogram, renal and hepatic profiles were normal. Mantoux test was positive at 11 mm. ESR was 20 mm / hour. CT scan chest and radiographs (Figs. 1-3) showed bilateral hilar, paratracheal and subcarinal lymph nodes. There were no parenchymal lung lesions. Pulmonary function test showed mild obstruction with restrictive ventilatory defect, and had no reversibility to inhaled salbutamol (FEV1 / FVC 41 / 56 % predicted and TLC 72%). Diffusion studies could not be done due to technical reasons). Echocardiogram showed thickened mitral valve leaflets with calcification, moderate mitral stenosis with mitral valve area of 1.9 - 2.1 cm^2, good left ventricular systolic and diastolic function, dilated left atrium, normal aortic and pulmonary valves and pulmonary artery systolic pressure of 42 mmHg. There was no pleural effusion. Bronchoscopy done showed no pigmentation, mucosal abnormality or stenosis. Bronchial lavage for acid fast bacilli culture, culture for microorganisms and cytology were negative.

Mediastinoscopy and biopsy of the pretracheal and paratracheal lymph nodes was done. Histopathology showed mild to moderate degree of anthracosis, secondary follicles with germinal centers, proliferation

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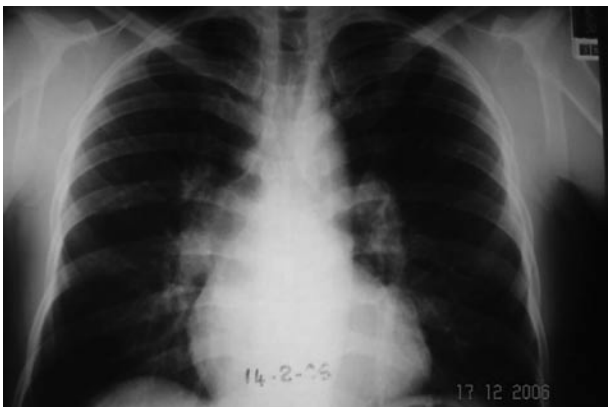

Fig. 1: X-Ray chest showing mediastinal adenopathy

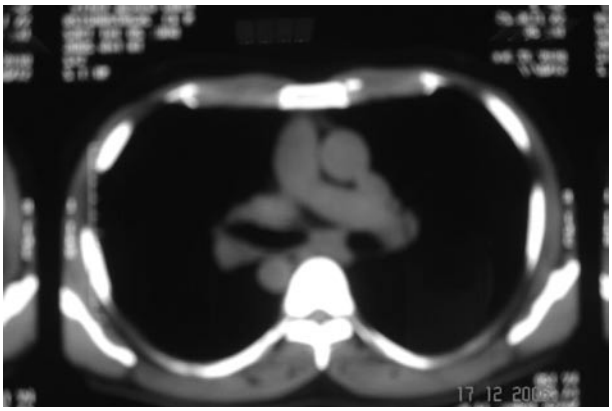

Fig. 2: Thoracic CT scan showing mediastinal lymph nodes

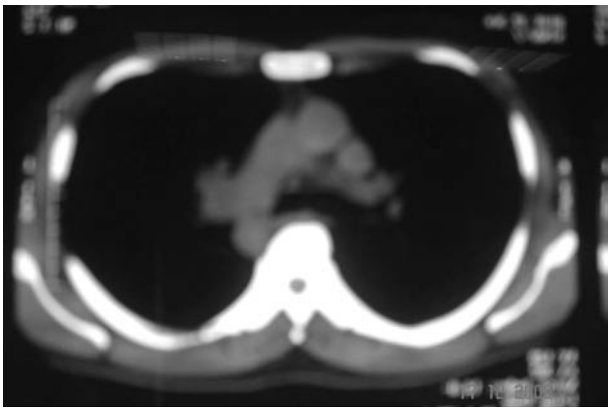

Fig. 3: Thoracic CT scan showing mediastinal adenopathy

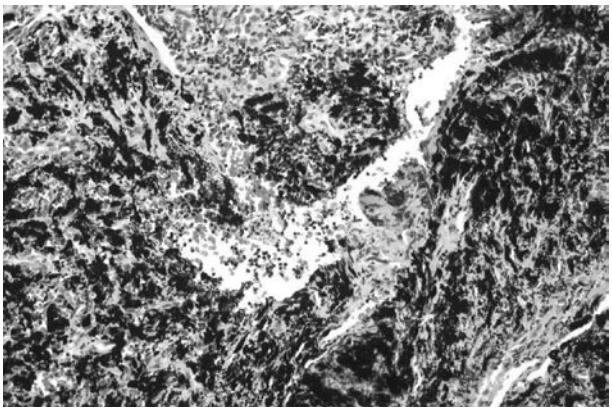

Fig. 4: High power microscopy of lymph node showing anthracotic pigments with reactive follicles

of histiocytes and plasma cells and normal relation between B and T lymphocytes. No granulomas were seen (Fig. 4).

DISCUSSION

Anthracosis is a form of pneumoconiosis caused by coal dust or by a smoky polluted environment. Pulmonary anthracosis, in particular, is well-documented as coal workers' pneumoconiosis (CWP) in adults[1]. The term anthracotic is usually used to describe coal and other black pigments of which carbon is a major constituent[2]. Characteristically, coal deposits present as black plaques in the bronchi of coal miners and, rarely, in city dwellers[3].

One other reported cause for anthracosis is exposure to cigarette smoke[4,5]. In studies by Chung *et al* and Mirsadree *et al*, 71% and 81% of patients with anthracofibrosis were non-smokers, indicating that smoking is not the prime risk factor[6,7]. Exposure to smoke from bio-mass fuelled fires, in rural areas of third world countries, has been reported as a cause for anthracosis of lung[5,8-10]. The terms 'hut lung' or 'domestically acquired particulate lung disease' (DAPLD) has been used for this particular condition[5,10]. Tuberculosis and malignancy were also implicated as background for anthracosis[3,6,11-13]. Argani *et al* and Varghese *et al* have reported cases of anthracosilicotic spindle cell pseudotumor which mimicked a neoplastic process clinically, radiologically and pathologically[14,15].

Anthracosis though often presents in the pulmonary form and rarely as mediastinal adenopathy; extrathoracic cases, like esophageal anthracosis, axillary lymphadenopathy and hepato-splenic anthracosilicosis have been reported[16-18].

Patients with anthracosis are usually asymptomatic or present with cough, dyspnea and hemoptysis[6,7]. Plain chest radiographs may show consolidation, reticulonodular lesions, atelectasis, hilar adenopathy or mediastinal widening. Involvement of upper, middle and lower lobes is reported[6,11]. Bronchoscopy in these patients shows anthracotic pigmentation of bronchial mucosa which is usually extensive. When associated with inflammation and bronchial luminal narrowing, the term anthraco-fibrosis is used[6]. Antharcotic pigments can be seen in bronchoscopic biopsy specimens and broncho-alveolar lavage cytology. Anthracosis often causes intrapulmonary lymphadenopathy (IPLN)[19]. Video assisted thoracic surgery is required to exclude malignancy in these cases[20]. Intrathoracic lymphadenopathy following tuberculosis is relatively common in Asians and Africans, and these are often anthracotic in aged

individuals[7].

This case is reported because of the presentation as huge mediastinal lymphadenopathy which was not reported previously in literature, and the postulation that the cause for anthracosis in this case is exposure to smoke from burning oil wells during the Gulf war.

CONCLUSION

This is a rare case of anthracosis proved by mediatinoscopic biopsy, caused by exposure to smoke during the Gulf war and presented with huge mediastinal lymphadenopathy.

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Case Report

Arthrogryposis, Renal Tubular Dysfunction and Cholestasis (ARC) Syndrome: A Case Report

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ABSTRACT

Arthrogryposis, renal tubular dysfunctions and chloestasis (ARC) syndrome is a rare multisystem, usually fatal, autosomal recessive disorder. Awareness of this syndrome is growing with more reported cases over the last three decades. Many previously reported cases with similar association are now labeled as ARC syndrome. Although the genetic mutation is recently recognized, the diagnosis still depends on the clinical findings.

Our patient is the first case of ARC syndrome to be reported from Kuwait. To the best of our knowledge this is also the first report of an Egyptian family with two siblings of ARC syndrome.

KEY WORDS: arthrogryposis, cholestasis, renal tubular acidosis

INTRODUCTION

Arthrogryposis, renal tubular dysfunction and cholestasis (ARC) syndrome (OMIM 208085) is a relatively rare, multisystem disorder. To date, 63 patients from 36 pedigrees have been reported. The pedigree of the patients supports an autosomal recessive inheritance[1, 2].

It has become obvious over recent years that the phenotypic expression of the disorder is variable and expanding[3]. Some cases may go undiagnosed as not all the three cardinal features of the disease are present or appreciated in all patients[4].

CASE HISTORY

A 35-day-old female child was admitted for further evaluation of direct hyperbilirubinemia. She was the second child to a first cousin Egyptian couple; she was born at term after an uneventful pregnancy and delivery. Her birth weight was 4 kg. Jaundice was observed at the age of seven days but medical advice was not sought.

Parents reported that their first baby, who was also a female, developed cholestatic jaundice early in life. She was failing to thrive with microcephaly, multiple joint contractures, rocker bottom feet, and ichthyosis. Extensive investigations failed to reveal the underlying problem. She got repeated infections and died suddenly at age of seven months.

Clinical examination of our patient showed that she had some facial dysmorphic features in the form of upward slanted eyes, low set ears and flat nasal bridge, with contractures at both knees and hips and dry scaly skin (diagnosed later as ichthyosis). She was clinically jaundiced with failure to thrive (weight 3.6 kg).

The laboratory investigations showed direct hyperbilirubinemia (total serum bilirubin was 180 umol/l and the direct serum bilirubin was 105 umol/l), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were mildly raised (109 U/l and 85 U/l respectively). Serum alkaline phosphatase (ALP) was markedly raised (1263 U/l) with normal Gamma glutamyl transpeptidase (GGT) on many occasions.

The other laboratory results including screening for inborn error of metabolism, congenital infections, hypothyroidism, cystic fibrosis, chromosomal studies, and Alpha 1 antitrypsin, were all unremarkable. X-ray of the spine, cranial computed tomography (CT) and echocardiography were also normal.

Radio-isotope (HIDA) scan for biliary system showed evidence of cholestasis. The liver biopsy showed evidence of giant cell hepatitis with bile ducts proliferation (Figs. 1 and 2).

She continued to be 'failing to thrive' in spite of feeding her a fully hydrolysed milk formula, multivitamins, and medium chain triglycerides. At the age of two and half months the child developed fever and submandibular lymph node abscess. The abscess aspirate grew *Pseudomonas aeruginosa*. She was

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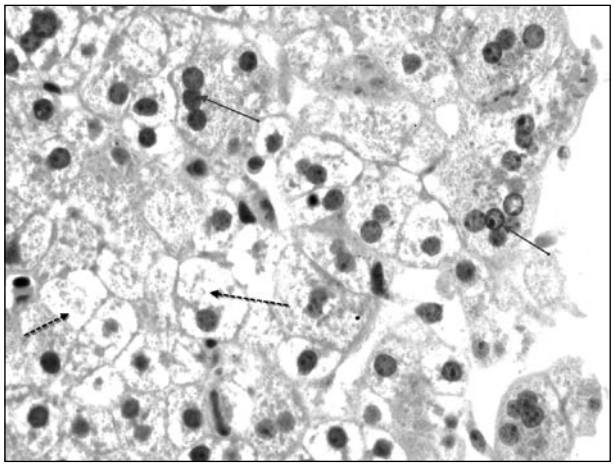

Fig. 1: H/E stain liver biopsy slide showing giant cell hepatitis with preserved hepatic architecture and fatty changes (doted arrows) of hepatocytes and giant cell formation (solid arrows)

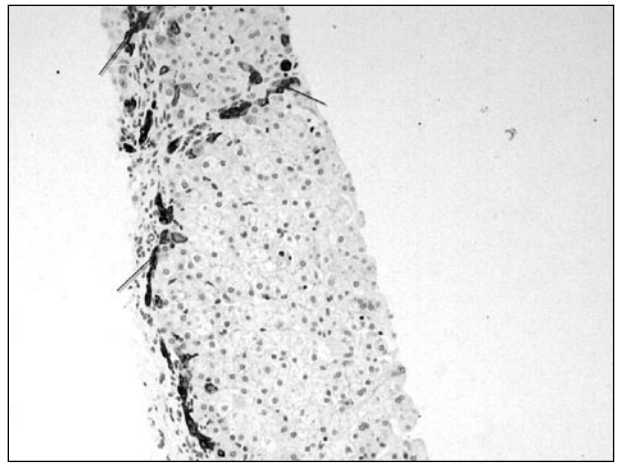

Fig. 2: CK immuno-histochemical stained liver biopsy slide showing bile ducts proliferation (arrows) with preserved hepatic architecture

admitted to the hospital and started on intravenous antibiotics. In spite of the initial improvement the fever recurred. Her arterial blood gases showed mild metabolic acidosis (pH 7.25, PCO_2 4.03 kPa) with a normal anion gap of 8 mmol, high chloride level (123 mmol/l), and alkalotic urine (pH 8), a picture suggestive of renal tubular acidosis.

Her general condition worsened with food intolerance, significant abdominal distension and blood-stained stool. Abdominal ultrasound study and cross table X-ray abdomen revealed evidence of necrotizing enterocolitis. The child was shifted to the pediatric intensive care unit where oral feeding was withheld. Total parental nutrition and sodium bicarbonate were commenced in addition to the intravenous antibiotics.

A picture of Fanconi syndrome with glucosuria, (in spite of normal blood sugar), aminoaciduria, phosphaturia and hypophosphatemia developed.

There were repeated episodes of hypernatremia with polyuria. Blood osmolality was high (349 mOsm/kg) with low urine osmolality (198 mOsm/kg). Nephrogenic type of diabetes insipidus (DI) was suspected as she failed to respond to intravenous desmopressin (DDAVP).

In spite of full medical support the child's condition deteriorated. She developed multi-system failure and died at the age of three and half months.

The diagnosis of ARC syndrome was based on the clinical picture, laboratory findings and the family history.

DISCUSSION

ARC syndrome was first documented in 1973 by Lutz-Richner *et al*[5]. A number of case reports have been published since then[6-8] which have been recently labeled as ARC syndrome. Consanguinity and affected membership are typical finding in most reported cases of this rare syndrome. This makes autosomal recessive transmission a considerable possibility[1].

Though the gene mutation of the disease has been recently recognized[9] the diagnosis still depends on clinical findings. The three cardinal features of the disease (arthrogryposis, renal tubular dysfunction, cholestasis with normal GGT) might not be evident or appreciated at the same time[3]. This, combined with the fact that most patients die early (in the first six months of life)[2] and unawareness of the disease because of its rarity, may lead to missing the diagnosis in many cases. This was probably the case of our patient's sister who died early in life.

The phenotypic expression of the disease is expanding and variable even in the same family. Features like cerebral malformation, congenital heart disease, abnormal large platelet, nephrogenic DI, ichthyosis, failure to thrive, facial dysmorphism and recurrent infections are reported[1,3,10]. All (except the first three features) are documented in our patient.

Cholestasis is a constant and early feature of ARC syndrome. The level of serum bilirubin varies between patients and even in the same patient with time; ranging from significantly high (300 umol/l) to normal values. Though ALP was high, GGT was consistently normal in all reported patients (and also in our case). Other liver enzymes were normal or slightly raised in all reported patients [1].

Liver histology is variable in patients with ARC syndrome. Some showed cholestasis with giant cell transformation (as in our patient), while others showed intra-hepatic biliary hypoplasia with lipofusin deposit. The site and time of the biopsy generally influence the findings[3]. Normal liver biopsies are occasionally reported[11].

Arthrogryposis in ARC syndrome appeared to be partially neurogenic in origin[3]. The degree of joint contractures depends on fetal position *in utero* and severity of oligo-hydramnios. It ranged from isolated talipes to severe generalized form including congenital hip dislocation[1].

Bull *et al*[4] reported one patient with classical ARC features who had only rocker bottom feet with no arthrogryposis. Bilateral knee and hip contractures were observed in our patient and also reported in her sister with rocker bottom feet.

Renal tubular dysfunctions, ranging from isolated renal tubular acidosis to frank Fanconi syndrome, are reported in all patients with ARC syndrome. This may manifest in the first few days of life or later (around 2 - 3 months of age)[1,3]. Nephrogenic DI was documented in our case and also in many other patients with ARC syndrome [1,2].

Ichthyosis, recurrent infections and sepsis (usually the cause of death in most patients), failure to thrive (secondary to fat malabsorption, renal tubular wasting, and high caloric demands due to recurrent dehydration and sepsis) and dysmorphic facial features are all documented in patients with ARC syndrome[1,3,4,11] and also seen in our patient.

Bleeding problems with life-threatening hemorrhage was observed in almost half of the patients (7/16) who underwent diagnostic (liver and renal) biopsies in spite of normal platelet count and coagulation profile [1,3,12].

The genetic background of ARC syndrome was not clear until Gissen *et al*[9] published their report which revealed its molecular basis. They mapped the disease to 7-cM interval on 15q26.1 and identified loss of function-mutation in VPS33B gene.

This gene encoded the synthesis of a specific protein (called VPS33B protein) which regulates vesicle- to-target membrane fusion that is necessary for secretions to occur. Deficient expression of this protein is linked to many of the features of ARC syndrome.

Hershkovitz *et al*[13] suggested that deficient expression of the VPS33B protein may interfere with normal epidermal differentiation in patients with ARC syndrome. This could explain ichthyosis in those patients.

Likewise, Mathews *et al*[14] in an animal study hypothesized that deficiency of VPS33B protein in biliary epithelial cell will affect its development and may explain cholestasis in patients with ARC syndrome. He also suggested that deficient expression of the same protein in patients' intestinal cells might impair lipid absorption; contributing to the universal finding of 'failure to thrive' that was noticed in almost all reported patients.

Lo *et al*[15] found that the platelets of patient of ARC syndrome were abnormally large in size and completely lacking the alpha granules, absence of which are known to be associated with congenital bleeding problem. They found that the VPS33P protein was absent in megakaryocytes of patient with ARC syndrome. They also concluded that the VPS33P protein is essential for the development of alpha granules in platelets. Absences of these granules would explain the bleeding disorder in patients with ARC syndrome.

CONCLUSION

ARC syndrome is not as rare as it was thought to be, and it should be included in the differential diagnosis of infants with cholestasis, especially in societies with high rate of consanguineous marriage and whenever other investigations fail to find an underlying etiology. The detection of germ line mutation of VPS33P gene might eliminate the need for diagnostic organ biopsy that carries a 50% risk of life-threatening hemorrhage due to platelet disorder. So far, no specific treatment for this syndrome is available and most patients do not live longer than seven months after birth in spite of supportive measures.

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Case Report

Pigmented Villonodular Synovitis: How to Make an Early Diagnosis

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ABSTRACT

Pigmented villonodular synovitis (PVNS) is a rare condition usually affecting the knee. It is a benign proliferative growth of the synovium of obscure etiology with a wide spectrum of clinical presentations. PVNS can be a difficult condition to manage, with an average delay in diagnosis of 4.4 years. We describe a case of diffuse form of PVNS in a young patient who presented with vague left knee complaints for two years.

KEY WORDS: giant cell tumors, hemarthrosis, tenosynovium

INTRODUCTION

Pigmented villonodular synovitis (PVNS) is an uncommon disease with an incidence of 1.8 cases per million people per year[1]. It is a proliferative disorder of the synovium. PVNS affects the large joints, knees and hips predominantly, with 67% cases involving the knee[1,2]. It occurs in two forms: a diffuse form that involves the entire synovium and accounts for the majority of cases, and a localized form that involves a discrete section of the synovium.

The speculated causes for PVNS are: (1) neoplasm (2) chronic inflammation or (3) abnormal lipid metabolism. However, the definite etiology remains unclear.

The most common clinical presentation of PVNS is intermittent deep joint pain, which is exacerbated by movement. Additional mechanical symptoms[3] can add to difficulty of making a diagnosis, with an average delay in diagnosis of 4.4 years[4]. Occasionally there is evidence of joint effusion with intermittent joint swelling.

We discuss the case history of a 45-year-old woman with a two-year history of left knee pain associated with intermittent swelling and limping. We discuss here the diffuse form of PVNS and highlight the importance of clinical and radiographic features in making an early diagnosis. We also emphasize on the importance of remembering this condition as a differential diagnosis in a young person with an unexplained monoarticular complaint.

CASE HISTORY

A 45-year-old woman presented to our rheumatology clinic with a two-year history of anterior left knee pain with intermittent clicking in the joint associated pain and joint swelling. She also reported intermittent limitation in range of motion and limping. She gave no history of locking, giving way, or trauma. She had no other joint problems and her past medical history was unremarkable. On examination, the left knee was swollen and warm, without erythema. Crepitus was felt and there was obvious reduction in the range of motion (ROM). She also experienced pain with knee flexion (during both passive and active ROM) more than 30 degrees. Synovial fluid analysis revealed non-inflammatory range of leukocytic count. The fluid was hemorrhagic. There were no crystals seen. Cultures and staining were negative for bacterial infection and tuberculosis.

Plain X-ray of the left knee revealed subchondral sclerosis, marginal osteophytes, joint effusion, erosion of the patellar articular surface and preserved joint space. There was no osteopenia (Fig. 1). MRI showed hypertrophic synovial nodules, bone erosions, moderate joint effusion and preserved joint space with absence of calcification (Figs. 2A & 2B).

Arthroscopic synovial biopsy revealed features compatible with PVNS, showing multiple pieces of soft yellow and tan colored tissue. Microscopic examination of the synovial tissue showed papillae composed of stromal cells, with multiple nucleated

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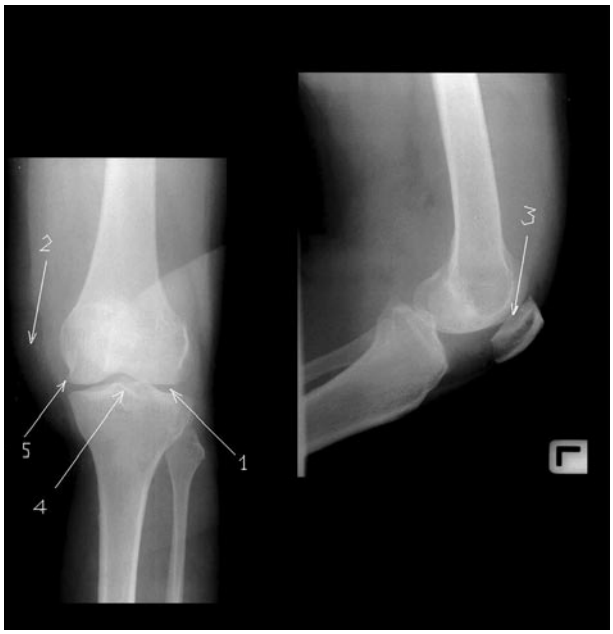

Fig. 1: AP and lateral view of the left knee showing: (1) preserved joint space, (2) joint effusion, (3) erosion of the posterior surface of the patellar articular surface , (4) subchondral sclerosis and (5) marginal osteophytes

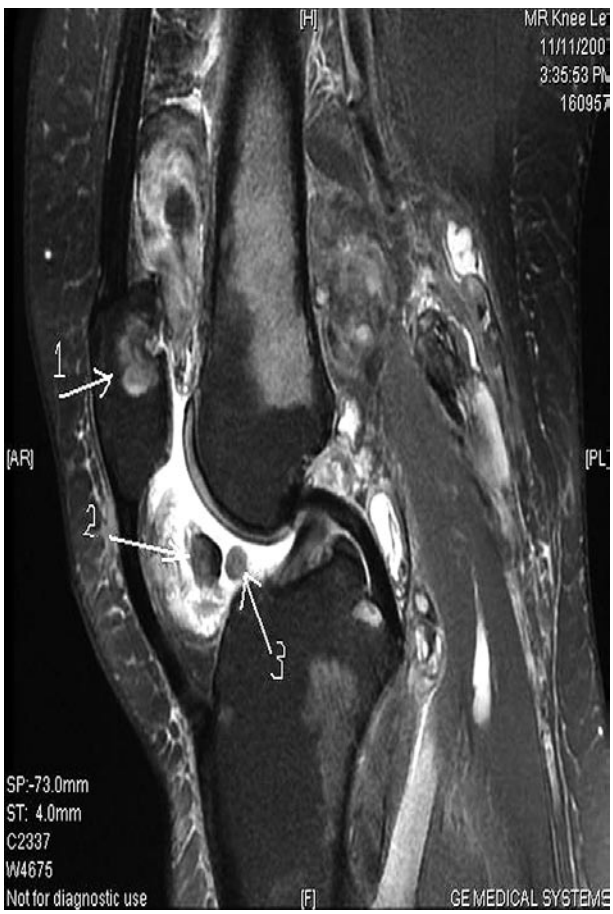

Fig. 2A: Sagittal proton density section of the left knee showing: (1) large heterogeneous lobulated intrasynovial mass in the supra-patellar recess, (2) erosion of the posterior patellar articular surface and (3) erosion of the Hoffa's fat pad by synovium

giant cells, hemosiderin laden macrophages, scattered lymphocytes and prominent vessels (Fig. 3).

The lesion was completely excised and removed through a small transverse incision under direct vision. At her six-month follow-up, the patient reported complete resolution of her symptoms, and her patella tracking was noted as normal.

DISCUSSION

PVNS is a proliferative disorder of the synovium. It is an uncommon disease with unknown etiology that affects patients at any age (usually 20 - 50 years). Symptoms are usually non-specific, *e.g.*, joint pain, warmth, and swelling, which can be intermittent and can lead to delay in making an early diagnosis. Certain clues in the patient's history should raise the clinician's suspicion for PVNS. As illustrated by this case, typically a patient in the third or fourth decade of life presents with vague monoarticular complaints which are alleviated by rest. The pain can be severe, and intermittent. These episodes of extreme pain may represent hemorrhage into the joint space. Patients may also report decreased active and passive range of

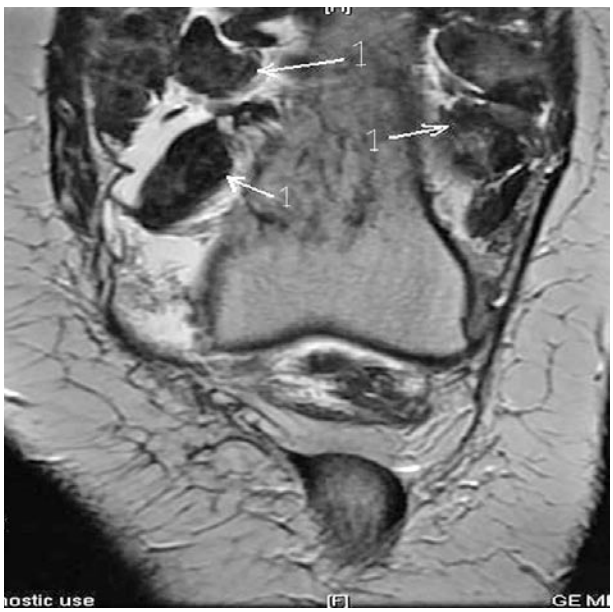

Fig. 2B: Coronal T2 section of the left knee showing multiple large intra- synovial masses

motion with normal exercise tolerance between these episodes of exacerbations.

It is important to make an early diagnosis of PVNS and to differentiate it from other commoner conditions that can present in a similar way. For example, patients with osteoarthritis can present with knee pain precipitated by activity and alleviated by rest, but this generally affects more than one joint and occurs in older patients. Another condition that can be confused with PVNS is chronic tuberculous

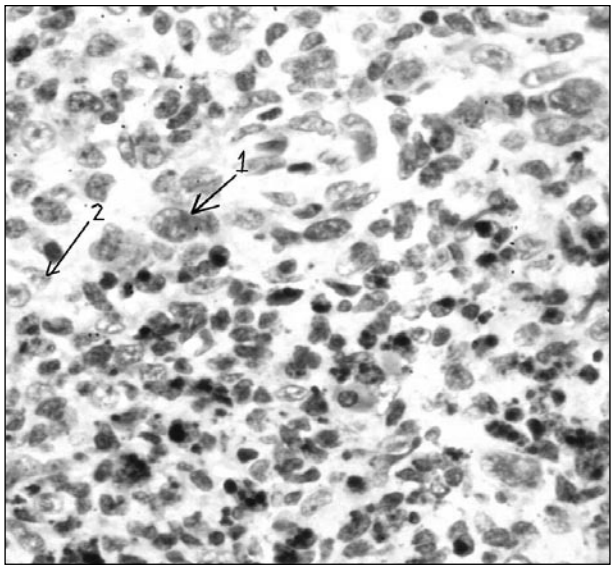

Fig. 3: Histopathology of synovial specimen showing: (1) multinucleated giant cells, (2) stromal cells and (3) brown granular deposits of hemosiderin

arthritis that can have a subtle presentation. The hallmark radiographic features of tuberculous arthritis include: juxtra-articular osteopenia, osseous erosions, and narrowing of the joint space. Other conditions that can cause hemarthrosis should be included in the differential diagnosis of PVNS *e.g*., hemophilia, hemochromatosis, and hemosiderosis. However, these conditions can be easily differentiated from PVNS by MRI and histological examination. Histologically the pigment in other conditions causing hemarthrosis is largely confined to the synovial cells and macrophages, whereas the distribution in PVNS is more diffuse. Giant cells and histiocytes seen in PVNS are not a feature of these other conditions.

An early diagnosis of PVNS can be made by recognizing classical features in history and arranging for the appropriate imaging studies. MRI is very sensitive and specific in detecting PVNS. It shows characteristic findings of joint effusion and synovial proliferation. The synovial lining has characteristic low signal areas on T1 and T2 weighted images correspond to areas of hemosiderin deposition[5-7]. Macroscopically, PVNS has a characteristic yellow-brown colour from hemosiderin deposition. Histological findings of PVNS include synovial proliferation and infiltration with multinucleated giant cells and macrophages[8,9]. Joint aspiration reveals blood stained synovial fluid 75% of the time and yellow fluid 25% of the time [7] .

CONCLUSION

PVNS should be considered in the differential diagnosis of young patients with vague monoarticular complaints.

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Case Report

Complete Laparoscopic Excision of Giant Mesenteric Cyst: A Case Report and Review of Literature

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ABSTRACT

Mesenteric cysts are rare intra-abdominal masses. To prevent complications, recurrence and possible malignant transformation, complete excision is considered to be the best option. We report a case of a 25-year-old woman with a giant mesenteric cyst which was completely excised by laparoscopy. A review of the literature is presented.

KEY WORDS: giant mesenteric cyst, intra-abdominal mass, laparoscopic excision

INTRODUCTION

Mesenteric cysts (MC) are defined as cystic masses located in the mesentery. The reported incidence of these lesions is approximately 1:100,000 in adults, 1:20,000 in children[1]. Since the first report of mesenteric cyst by Benevienal in 1507, more than 830 cases have been reported[1]. The first successful surgical resection was performed by Tillaux in 1880[2] while Mackenzie *et al* described the first case of laparoscopic excision of a mesenteric cyst in 1993[3]. Different treatment modalities have been discussed in the literature of which total cystectomy is the therapeutic method of choice. We present a case of giant mesenteric cyst which was successfully excised completely by laparoscopy and was removed from the same 12 mm port without extending the wound.

CASE REPORT

A 25-year-old married lady, a mother of three children, was referred from the gynecologist with a five-month history of an abdominal mass. The mass was discovered during pelvic ultrasound done by the gynecologist to check the position of her intra-uterine contraceptive device. On examination, there was a firm pelvi-abdominal mass measuring 20 x 15 cm. The mass was more on the right side and extending up to right lumbar area.

CT abdomen and pelvis showed a large intra-abdominal, multi-locular cyst measuring 19 x 10 x 13 cm extending from pelvis upward to the right hypochondrial area and causing displacement of the adjacent bowel loops and indentation of the urinary bladder. The mass was separate from ovaries and uterus (Figs. 1 and 2).

Laparoscopic procedure was done under general anesthesia with the patient in supine position. First trocar (12 mm) was inserted at the left upper quadrant using optic view. Other three trocars were inserted under direct camera vision as follows: 11 mm port at left lower quadrant; 5 mm port at suprapubic area; and 5 mm port at the right lower quadrant. A huge mesenteric cyst was seen, occupying the whole pelvis up to the lower edge of the liver, with its pedicle attached to the transverse mesocolon. Using the ligasure, the pedicle was divided from the superior aspect until full mobilization of the cyst. The cyst was totally resected without any damage to the adjacent intestinal segments or mesentery. There was no evidence of associated liver lesions or peritoneal implants. Ovaries and tubes were normal. Due to its big size, the cyst was placed in a large endobag. Partial deflation was done by puncturing the cyst with aspiration of the contents while still inside the bag and without any spillage. The edges of the bag were withdrawn from the left upper quadrant port and the cyst was externalized in pieces. The cyst had a honey comb like appearance with thick gelatinous material inside. The fascia of the left lower quadrant port was closed by suture passer under direct camera vision with 0-vicryl. Total operative time was about 110 minutes, of which 20 minutes was for the piecemeal removal of the cyst. She had uneventful post-operative period

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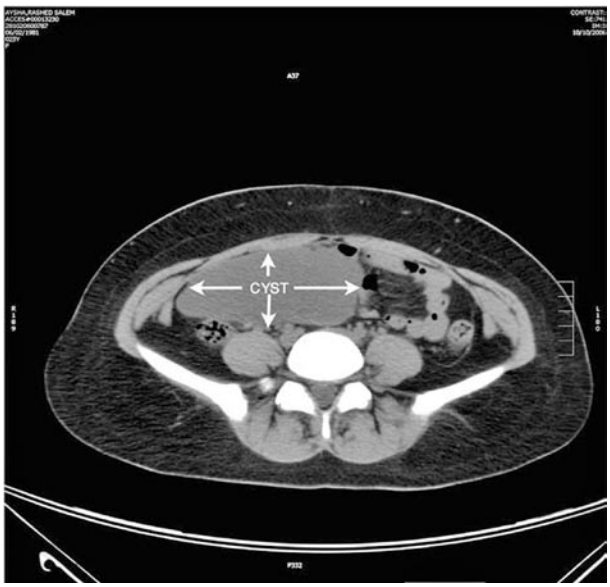

Fig. 1: CT scan abdomen showing the cyst causing displacement of adjacent bowel loops

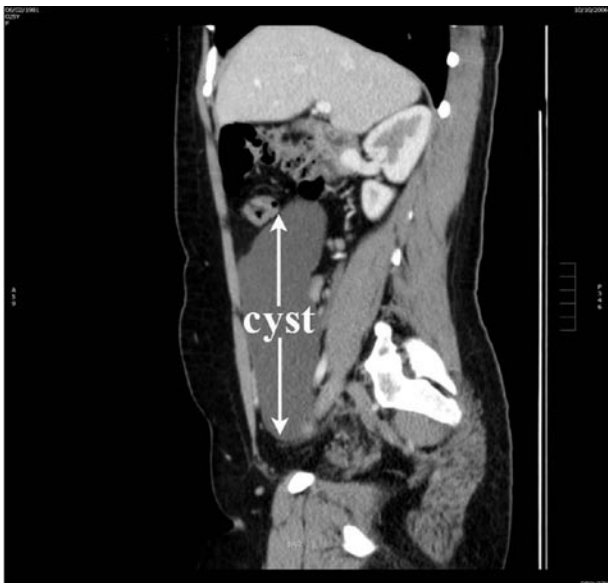

Fig. 2: Sagittal reconstruction showing the extent of the cyst from pelvis up to right hypochondrial area

and was discharged on the third post-operative day. The final histopathology report was consistent with multilocular mesenteric cyst. Patient was followed up in the surgical outpatient clinic with no complaints till one year post-operatively.

DISCUSSION

MC are a relatively rare intra-abdominal masses that can occur at any age; it is common in people between 40 and 70 years of age but it also affects children younger than age 10 years[4]. The etiology of lymphangiomas and benign cystic mesotheliomas has not been defined clearly. However, simple lymphatic and mesothelial cysts are mostly congenital. They can also be related to previous pelvic surgery, trauma, pelvic inflammatory disease, endometriosis and neoplasia[5-7]. The most frequent site is the mesentery (60%), followed by the mesocolon (24%), and the retroperitoneum (14.5%), while it is indefinite in 1.5% of cases[8]. In our case, it was attached to the transverse mesocolon. Other reported rare site that MC can originate from is the stomach[9]. Hernias containing MC are also reported such as strangulated recurrent umbilical hernia[1] and indirect inguinoscrotal hernia[10].

The differential diagnosis for cystic lesions in the mesentery includes lymphangioma, pancreatic pseudocysts, hemangioma, endometriosis, loculated ascites (usually tuberculous), peritoneal inclusion cysts, cystic mesenteric panniculitis (sclerosing mesenteritis), hydatid cyst, cystic teratoma and urogenital cysts.

MC usually ranges in size from a few centimeters to 10 cm but it can be very large[4,11]. In our case the cyst size was 19 x 10 x 13 cm. A cyst this large is fairly uncommon. Only two cysts bigger than ours are reported in the recent reviews sized 30 × 20 × 10 cm[11] and 23 x 15 x 3 cm[12]. Both were excised by laparotomy. To our knowledge, this is the first reported giant mesenteric cyst that was totally excised by laparoscopic methods without the need to extend the wound or pre-operative aspiration of the content[13]. Cysts can be unilocular or multilocular, and may contain chylous, serous or infrequently hemorrhagic fluid. In our case it was multilocular containing gelatinous transparent material. Mesenteric cysts filled with milk of calcium have been described[14], and there have also been rare reports of gas accumulation within cysts[15]. Different classifications of mesenteric cysts have been proposed but de Perrot *et al*'s[5] classification, which is based on histopathological features, is usually preferred now (Table 1).

Table 1: de Perrot classification of mesenteric cyst[5]

Origin	Type
1. Cysts of lymphatic origin	a. Simple lymphatic cyst b. lymphangioma
2. Cysts of mesothelial origin	a. Simple mesothelial cyst b. Benign cystic mesothelioma c. Malignant cystic mesothelioma
3. Cysts of enteric origin	a. Enteric duplication cyst b. Enteric cyst
4. Cysts of urogenital origin	
5. Mature cystic teratoma	Dermoid cyst
6. Non-pancreatic pseudocysts	a. Traumatic origin b. Infectious origin

Although mesenteric cysts are usually diagnosed incidentally during routine abdominal examinations, they can present as acute abdominal pain, chronic abdominal pain, nausea and vomiting, or change in bowel habit. Although rare, shock due to rupture or

bleeding of the cyst, intestinal obstruction secondary to external compression and volvulus or torsion of the cyst have been reported[5,7]. Our patient was discovered incidentally during pelvic ultrasound done by gynecologist to check the position of intra-uterine contraceptive device. Rupture of the MC due to blunt abdominal trauma is also reported[16].

Preoperative diagnosis is made using US, CT scan, and MRI. The role of radiological techniques is to demonstrate the abdominal mass with its size, determine the organ from which the mass originates, and to determine the relationship with surrounding organs[4]. MRI gives more precise imaging compared to CT scan.

Mesenteric cysts should be treated when they become symptomatic or when they cause complications. Surgery can prevent complications, such as rupture, bleeding, intestinal obstruction, volvulus, torsion and infection. Treatment options for mesenteric cyst are simple drainage, external or internal excision, enucleation, and external or internal marsupialization[5,7,17]. The mainstay of treatment is surgical removal of the cyst to avoid malignant transformation[5,7,18]. Excision of the cyst with segmental resection of involved bowel may be required in some patients[5,7]. If radical surgery is not technically possible, the cyst should at least be marsupialized, despite the acceptable risk of recurrence, infection, and fistulization involved. Simple aspiration or internal drainage of the cyst is not advised because of the high recurrence rate and risk of infection[8].

Possible drawbacks of laparoscopic treatment are the reported 3% incidence of malignancy[18-20] and the uncertainty of preoperative diagnosis.

CONCLUSION

Currently, complete laparoscopic cyst excision can be performed without any complications in appropriately selected patients and performed by well-trained laparoscopic surgeons.

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Case Report

Brucellosis-induced Isolated Thrombocytopenia: A Case Report

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ABSTRACT

Brucellosis is a multisystem disease usually presenting with a wide spectrum of clinical and laboratory manifestations. Hemtological manifestations are many and may include anemia, thrombocytopenia and / or leucopenia. In rare cases, thrombocytopenia can be severe and may result in bleeding into the skin and other mucosal sites. Prompt recognition of this complication and aggressive therapy are essential, since the mortality associated with bleeding into the central nervous system is considerable. In this short case report, we present a young patient with hematuria and thrombocytopenia associated with acute brucellosis. Thrombocytopenic purpura in this case did not respond well to high-dose intravenous immunoglobulin; however, treating the underlying acute infectious process resulted in a dramatic clinical and hematological improvement.

KEY WORDS: brucellosis, leucopenia, systemic infection

INTRODUCTION

Systemic infections are a frequent cause of thrombocytopenia as a result of several possible pathogenetic mechanisms. Such mechanisms include hypersplenism, defective bone marrow production, direct damage and clearance of platelets by viruses or bacteria, immune-mediated platelet destruction and hemophagocytic lymphohistiocytosis[1-4].

Brucellosis is one of the systemic infections that is known to cause a variety of non-specific hematologic abnormalities. It is primarily an infectious disease of animals, but humans contact the disease through either direct or indirect contact with infected animals. *Brucella melitensis* is the most invasive species and produces the most serious infection in humans and animals[5-6]. The infection due to *Brucella melitensis* in humans is most commonly due to the ingestion of fresh unpasteurized milk or its products obtained from infected goats, sheep, or camels.

In this report, we present a case of *Brucella melitensis* sepsis, which had an acute onset with clinical and hematologic findings mimicking thrombocytopenic purpura.

CASE HISTORY

A 25-year-old, previously healthy, Egyptian accountant male was admitted to our hospital with a five-day history of fever, backache, skin rash involving both lower limbs and passing red-colored urine. He denied any history of drug ingestion, consumption of dairy products or direct contact with infected animals. He also denied a recent travel or history of infectious disease or hospitalization.

Physical examination revealed a temperature of 39 ^{o}C, heart rate of 110 beats/minute, and a blood pressure of 130/80 mmHg. The patient looked slightly pale. Skin examination revealed petechial rash that was limited to both lower limbs. There was no evidence of bleeding from the buccal mucosa or gingiva. ENT examination was unremarkable. Abdominal examination did not reveal organomegaly. Examination of cardiovascular, respiratory and neurological systems was unremarkable.

The results of the laboratory investigations were significant for mild anemia and marked thrombocytopenia with a hemoglobin of 120 g/l, MCV of 85 fl, MCH of 28 pg, white blood cell count of 9 x 10^9/l with normal differential count, and a platelet count of 9 x 10^9/l. Reticulocyte count was within normal limits. The peripheral blood smear showed normocytic morphology, unremarkable white blood cell morphology and rare large platelet forms. No circulating abnormal cells were noted. The

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results of liver function test, serum total bilirubin, renal profile, were within normal limits. Serum levels of sodium, potassium, chloride, urea, uric acid, total protein and albumin were normal, and serum lactate dehydrogenase was within normal limits. Urinalysis was remarkable for hematuria. Coagulation profile was within normal limits. Abdomen and pelvic ultrasound confirmed the absence of organomegaly. Virology screen for hepatitis B, C, CMV, EBV and HIV were all negative, and so was the immunological screen by ANA testing.

The patient was initially diagnosed as a case of virus-induced immune thrombocytopenic purpura (ITP), and accordingly, high-dose intravenous immunoglobulins were commenced (1 g/kg body weight/ day for two consecutive days). The platelet count failed to show an increment by the 4th day of initiating immunoglobulin therapy. Bone marrow examination was performed and the aspirate showed active megakaryopoietic activity with plentiful morphologically unremarkable megakaryocytes. Bone marrow biopsy showed doughnut-ring granuloma (Fig. 1). Blood culture results subsequently revealed growth of *Brucella melitensis*. This was later confirmed by a positive agglutination test for brucellosis at a titer of 1:1, 280.

The patient was accordingly started on rifampicin (600 mg/d) and doxycycline (200 mg/d), to which he responded dramatically with a progressive rise in his platelet count over a period of one week. His fever started to subside two days after the initiation of antibiotic therapy. He was discharged in a good general condition and a normal platelet count and hemoglobin level. He was advised to attend the Infectious Diseases Hospital (IDH) for follow-up and be re-evaluated after concluding his six-week antibiotic therapy course. He remained well clinically and hematologically.

DISCUSSION

Brucellosis is a multi-system infectious disease leading to changes in hematological parameters. Its diagnosis is based on a positive Wright agglutination reaction or positive blood or bone marrow cultures. The most frequently observed hematological abnormalities in brucellosis are mild anemia, neutropenia and / or thrombocytopenia. The latter, being usually mild, is relatively common, and has been reported in 1-8% of cases[7-11]. Hemorrhages have been reported in 3 - 19% of patients with brucellosis[8]. These were more frequently associated with *B. melitensis* than with other Brucella species. The mortality rate, however, is as high as 9.3%[6]. The mechanism responsible for thrombocytopenia in brucellosis remains obscure; however, among the many proposed possible mechanisms are hypersplenism, disseminated intravascular coagulation (DIC), bone marrow suppression, hemophagocytosis, endotoxin-induced platelets clearance, immune-mediated platelets destruction and clearance, and platelet adherence to vascular endothelium[8].

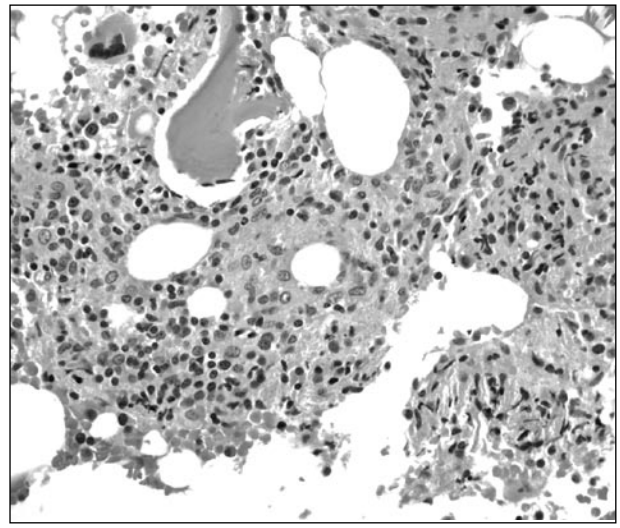

Fig. 1: Bone marrow biopsy section, showing donut-ring granuloma. Paraffin-embedded, H&E X 390

Splenomegaly is reported to occur in around 20 – 40% of patients with brucellosis[6]. DIC is rare in patients with brucellosis when compared to patients with bacterial septicemia[10]. Brucella bacterial products (*e.g.*, endotoxins) that are released into the circulation can cause diffuse vascular involvement and endothelial damage, as part of the systemic nature of the infection, or bind to platelets causing them to aggregate and be removed from the circulation[8]. However, brucella endotoxin appears to be less toxic than are lipopolysaccharides from other gram-negative bacteria.

Bone marrow failure also seems to be one possible etiology although an unlikely explanation for thrombocytopenia in brucellosis, since in one series the majority of cases (63.3%) showed hypercellular marrows with prominent megakaryopoietic activity[12]. It is thought that Brucella species have a high affinity for the reticulo-endothelial tissue[7,8]. As shown by our patient's marrow picture, doughnut granulomas were seen (Fig. 1). These granulomas were reported in nearly 30% of brucellosis patients[12]. It is to be noted that the granulomas of brucellosis may be indistinguishable from those found in other diseases or infections, such as sarcoidosis, tuberculosis, listeriosis, histoplasmosis, cryptococcosis, malaria, toxoplasmosis, and leishmaniasis[12]. Brucella-associated granulomas tend to be small and poorly defined, and lack caseation necrosis[12]. However, the distinction between granulomas of brucellosis and those due to other infections is important, but it is not always possible based on histological examination alone. Therefore, the most reliable method of determining the nature

of granulomatous lesions in the bone marrow is by bacterial and fungal cultures of the marrow.

Another possible mechanism that has received attention recently is reactive hemophagocytosis[12]. The finding of hemophagocytic histiocytes in the marrow of patients with brucellosis has been reported with varying frequency, and their significance remains conjectural. Furthermore, activated macrophages and granuloma formation in the bone marrow may also be implicated in patients with brucellosis. It could be suggested that the activated macrophages played some role in shortening the lifespan of circulating platelets[9,12].

Immune destruction of platelets has been considered to be responsible for thrombocytopenia in brucellosis[12], and the presence of antiplatelet antibodies has been demonstrated in some patients with thrombocytopenic purpura[12]. Evidence for an immune mechanism includes the apparent response to corticosteroids and / or intravenous immunoglobulins[13,14]. Antiplatelet antibodies may cause peripheral immune destruction of platelets, but it is difficult to detect these antibodies with the usual tests in brucella-induced thrombocytopenia. A negative assay for antiplatelet antibodies does not exclude the diagnosis of immune thrombocytopenia[14,15].

We believe that the mechanisms of thrombocytopenia in the acute brucella infection in our patient is multi-factorial including endotoxin-induced increased clearance of damaged platelets and ineffective megakaryopietic activity in view of the prominent megakaryopoietic activity and lack of response to intravenous immunoglobulins.

Brucellosis-induced thrombocytopenia, regardless of its pathogenetic mechanism, may significantly threaten life. However, with the availability of effective therapy, the mortality rate associated with brucellosis has declined to 1 – 2%[12]. Previous reports have demonstrated that platelets recovery usually occurs within one to three weeks of initiating appropriate antimicrobial therapy[16,9] .

CONCLUSION

Thrombocytopenia, like other hematologic complications of brucellosis, is generally mild and resolves promptly with treatment of the disease. In rare cases, thrombocytopenia can be severe and may result in bleeding into the skin and from mucosal sites. Prompt recognition of this complication and aggressive therapy are essential, since the mortality associated with bleeding into the CNS is considerable.

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Case Report

Pancreas Sparing Duodenectomy and a Proposal of a New Technique for Duodenum Reconstruction with a Pedicled Ileal Loop

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ABSTRACT

We present a new technique of duodenal reconstruction in selected cases of superficial epithelial tumors and gastrointestinal stromal tumor (GIST) of the duodenum thus avoiding the usual pancreaticoduodenectomy. Two cases of pancreas sparing duodenectomy were performed; one for severe dysplasia and adenoma and another for GIST. The duodenal reconstruction was done with a pedicled loop of ileum. Pancreas sparing duodenectomy is a safe procedure and could be a surgical option in selected cases of non-invasive tumors of duodenum.

KEY WORDS: duodenum, gastrointestinal stromal tumor, neoplasm

INTRODUCTION

Duodenal neoplasms are rare. Malignant tumors of the small intestine represent only about 1.5% of all gastro-intestinal (GI) malignancies[1]. They are categorized into four types, namely, carcinoid tumors (33%), adenocarcinomas (33%), lymphomas (20%) and GI tumors or GIST (10%)[1,2]. As far as duodenal neoplasms are concerned carcinoids and lymphomas represent roughly 5%, adenocarcinomas 48.4% and GIST 17.7% of these tumors[2]. Unfortunately, adenocarcinomas (non-ampullary tumors) or GIST of the duodenum are mainly advanced cases. Most of the adenocarcinomas have nodal or distant metastasis at time of operation and the five year survival is as low as 10%[2,3]. When these tumors are operable, pancreatoduodenectomy is performed but this procedure may be excessive for the superficial epithelial neoplasia or GIST. Pancreas sparing duodenectomy could be an option[4]. After partial or total duodenectomy reconstruction of the duodenal defect must be performed. Complexity of the reconstructive surgery depends on whether the ampulla of Vater is involved in the resection.

CLINICAL PRESENTATION AND EVALUATION

Case 1:

A 42-year-old Kuwaiti male presented with upper abdominal discomfort of five months duration. An upper GI tract endoscopy revealed a large flat and pale mucosal lesion starting from the end of the first part of the duodenum to the beginning of the third duodenum with a small nodule about 0.6 cm above the ampulla of Vater. The papilla of Vater was free of disease. By endoscopic ultrasound the lesions were superficial. Multiple biopsies were taken and showed mild to severe dysplasia with cells with nuclei on the luminal position of the cells - architectural back to back appearance. The growth pattern was classified as tubular lesion suspicious of a micro-invasive adenocarcinoma. The nodule was an adenoma. Endoscopy had shown a normal stomach. The preoperative diagnostic modalities included workup for familial adenamatoid polyposis, Crohn's disease, celiac disease, peptic ulcer and cystic fibrosis. All the workup was negative.

The patient was operated through a midline anterior abdominal wall incision. After a Kochers' manoeuvre, the head of pancreas and duodenum were exposed and consciously palpated. There were no masses, no suspicious regional lymph nodes and no liver or peritoneal metastasis (Figs. 1 & 2). The inferior vena cava was dissected free of all tissues preserving the gonadal vessels. The anterior branches of the inferior pancreatoduodenal vein were ligated and divided just below the pancreas. On the superior border of the pancreas, common hepatic artery was identified. At this site two lymph nodes on the hepatic pedicle were carefully dissected and sent for frozen section. All were free of metastasis. The gastroduodenal artery was preserved. Then the

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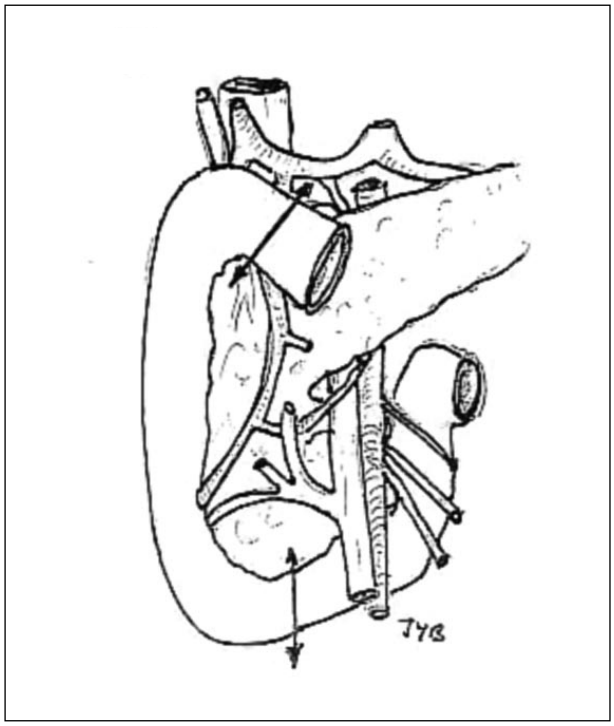

Fig. 1 A : Arrows show the sites of duodenal transection

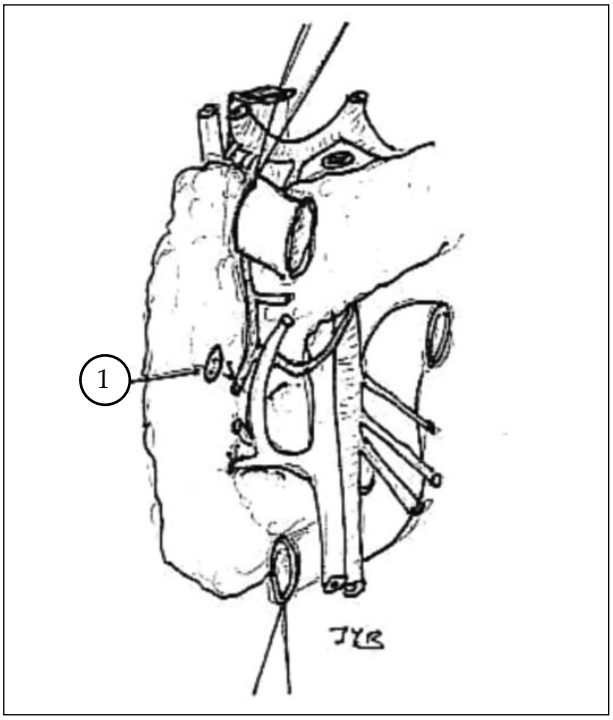

Fig. 1 B: The first, second and third duodenum were dissected from the pancreatic head
1 = Papilla

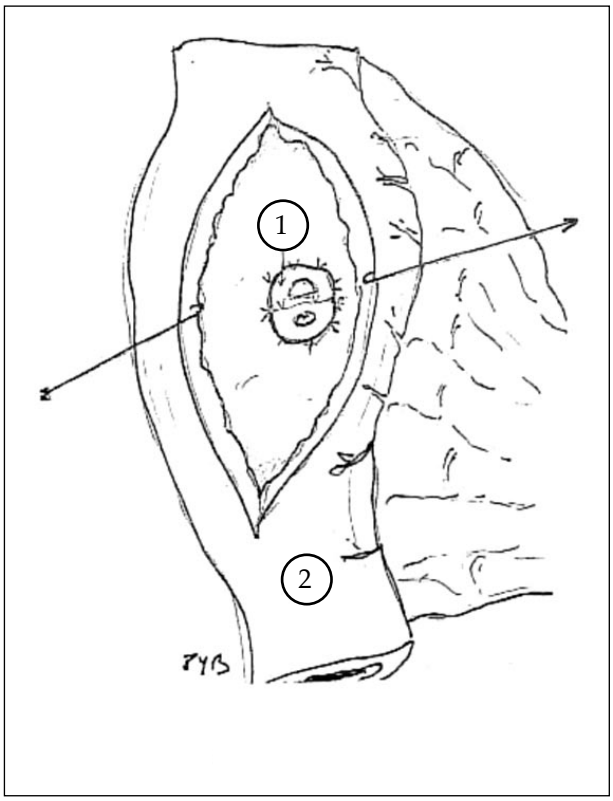

Fig. 1 C: Anastomosis of the papilla to the posterior wall of the pediculed ileal loop
1 = papilla; 2 = Pedicled ileal loop

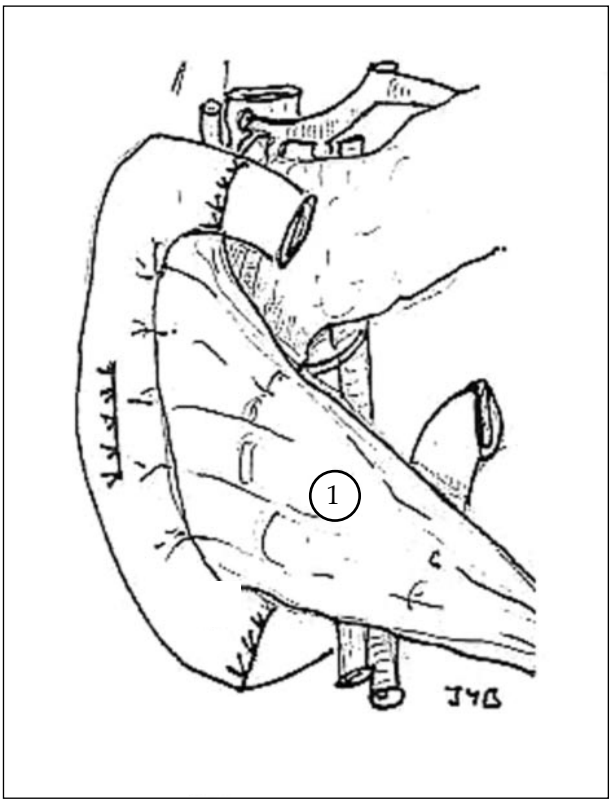

Fig. 1 D: Reconstruction of the duodenum with a pedicled ileal loop
1 = Mesenteric pedicle for the ileal loop

Fig. 1(a-d): Procedure steps of case number 1

first part of duodenum was transected at 1 cm after the pylorus. With great caution, the first, second and third part of duodenum was freed from the head of the pancreas. A careful hemostasis of all the small vessels was performed. An accessory pancreatic duct was ligated. At the end, the third part of the duodenum was transected 1 cm proximal to the superior mesenteric vein (Fig. 1a & b). The duodenal wall was divided around the papilla which was marked with a small catheter pushed down from the cystic duct. A 10 cm long pedicled ileal loop was prepared and passed through the transverse mesocolon up to the head of the pancreas. The reconstruction of the duodenum with this ileal loop was done by anastomosing the ileal loop with the remaining duodenum using 0000 maxon (R) (Fig. 1a - d). Then a 2 cm antimesenteric incision of the ileal loops was done at the level of the ampulla of Vater marked with the catheter. The posterior wall of ileal loop wall was opened (0.5 cm) and the papilla of Vater was fixed to the ileal loop wall with 0000 Maxon (R) (Fig. 1a & c). The catheter in the common bile duct was removed, the incision on the antimesenteric opening of the ileal loops was repaired, and a cholecystectomy was performed. All frozen sections performed on the margins of duodenal resections and on the edges of the papilla of Vater were free of disease. The abdominal wall was closed after putting a suction drain behind the head of the pancreas. Operating time was 210 minutes and blood loss 500 ml. On the second postoperative day the patient developed a small pancreatic fistula (less than 200 ml per day) which stopped spontaneously eight days later and was probably due to an accessory pancreatic duct. The nasogastric tube was removed on the fourth postoperative day and fluids started on the fifth postoperative day. Thereafter, he was started on a soft, low fat diet. He was discharged on the 12th postoperative day and advised to continue a low fat diet for one month. Pathology results had shown a mild to very severe dysplasia of all the mucosa of the duodenum but all margins were free of the disease with good free margins (> 1 cm). No micro-invasive adenocarcinoma was found. Four lymph nodes removed were free of metastatic deposits. The nodules near the upper part of the ampulla of Vater were a tubulous adenoma.

The patient is on regular follow up with endoscopy every six months for the first five years and then on with an endoscopy every year (last endoscopy December 2007). No recurrence was found and the patient returned to a normal life.

Case 2

A 62-year-old Egyptian gentleman with multiple co-morbidities (obesity, diabetes type II, hypertension, severe sequelae of myocardial ischemia) had hemoptysis in November 2005. Upper GI endoscopy revealed an ulcerated mass protruding into the lumen from the wall of the second part of duodenum, below the papilla of Vater reaching upto the beginning of the third part of duodenum (measuring 3 cm x 3.5 cm) occupying 50% of the duodenal lumen. The centrally ulcerated mucosa had a mild ongoing hemorrhage controlled with injection of 8 ml epinephrine (1/10,000 dilution). The patient was then sent to the cardiologist and hematologist for management of his co-morbidities. The patient was considered a high risk for surgery. A biopsy of the mass on 25/1/06 revealed duodenal GIST (CD 117+, CD 34 + and SMA+), S110 protein negative, mitotic count > 5 per hpf and dense cellularity; it was classified as an intermediate behaviour tumor. The patient was again sent for management of his severe co-morbidities. Imatinib 600 mg was started on 10/7/06 as neoadjuvant therapy. Until April 2007, he took imatinib with good tolerance with shrinkage of the duodenal tumor. However in April 2007, the tumor started to grow again. Thus, surgery was indicated but due to its radical nature, the aim was to avoid pancreaticoduodenectomy as much as possible in this fragile patient. At exploration on the 3rd of June 2007 through a right subcostal abdominal wall incision, the liver was found to be free of metastatic deposits. No suspicious regional lymph nodes were palpable. After Kocher manoeuvre, the duodenum and the head of the pancreas were exposed and consciously palpated (Figs. 2a & b). At the junction of the second part of duodenum and beginning of the third part of the duodenum, a nodular mass could be palpated opposite the head of the pancreas. The head of the pancreas was clinically free. The papilla of Vater was marked with a catheter pushed down through the cystic duct. The second part of duodenum was transected obliquely so that the upper part of the ampulla of Vater remained attached to the duodenal wall (Figs. 2a - c).

The third part of duodenum was divided 1 cm above the superior mesenteric vein. Then with great caution, the duodenal wall was freed from the head of the pancreas. All the small vessels between the pancreas and the duodenum were tied. A good hemostasis could be achieved. The removal of the mass was achieved by a full thickness excision of the second duodenum and 2/3rd of the third part of the duodenum. The duodenal defect was repaired with a 6 cm long pedicled ileal loop passed through the transverse mesocolon up to the head of the pancreas. The margins of the specimen were free of disease at frozen section. Reconstruction of the duodenum was done with the ileal loop by end to end anastamosis (Figs. 2b - d). The lower end of the ampulla of Vater was fixed to the posterior wall of the ileal loop. The

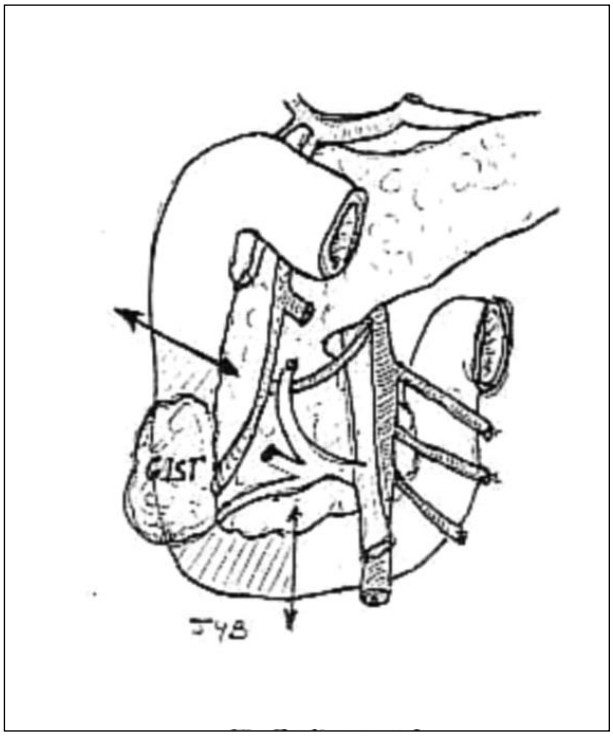

Fig. 2 A: Sites of duodenal transection

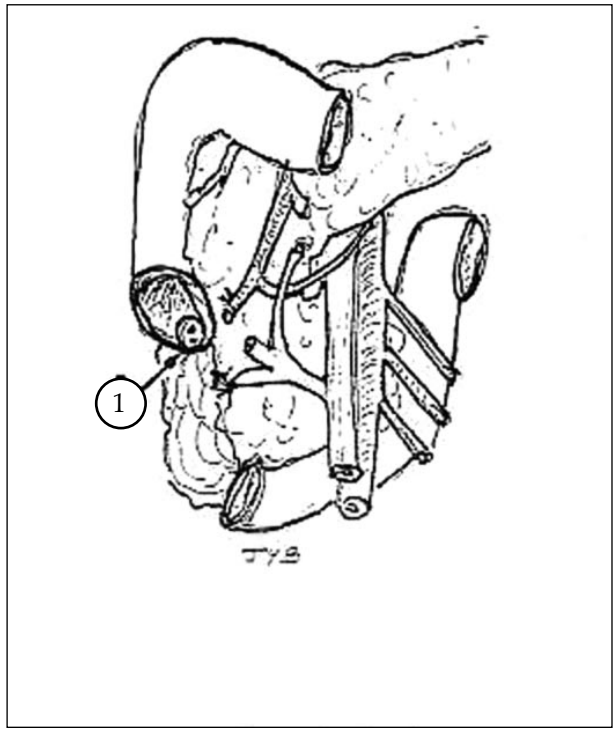

Fig. 2 B: A part of the second duodenum and third duodenum were removed. The papilla was exposed with its upper border still attached to duodenal wall.
1 = Papilla

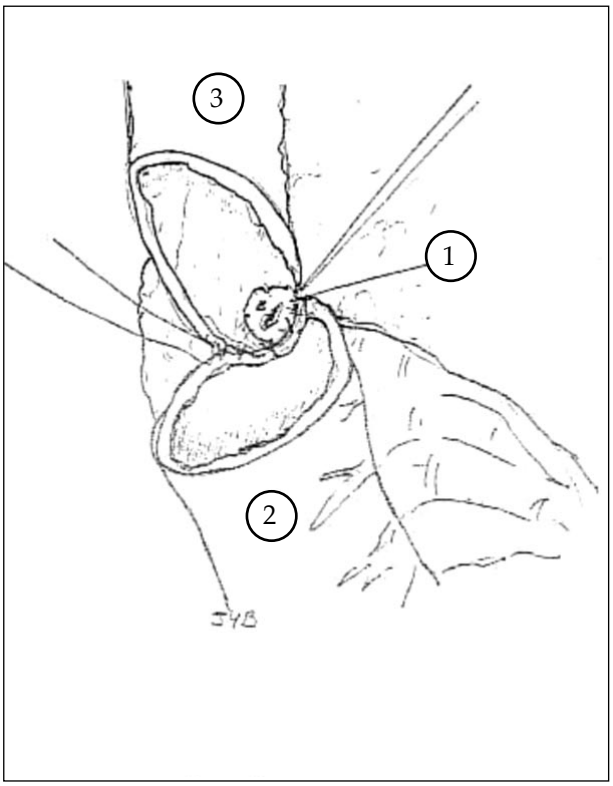

Fig. 2 C: Anastomosis of the papilla with the posterior wall of the pedicled ileal loop
1 = Papilla ; **2 =** Pedicled ileal loop

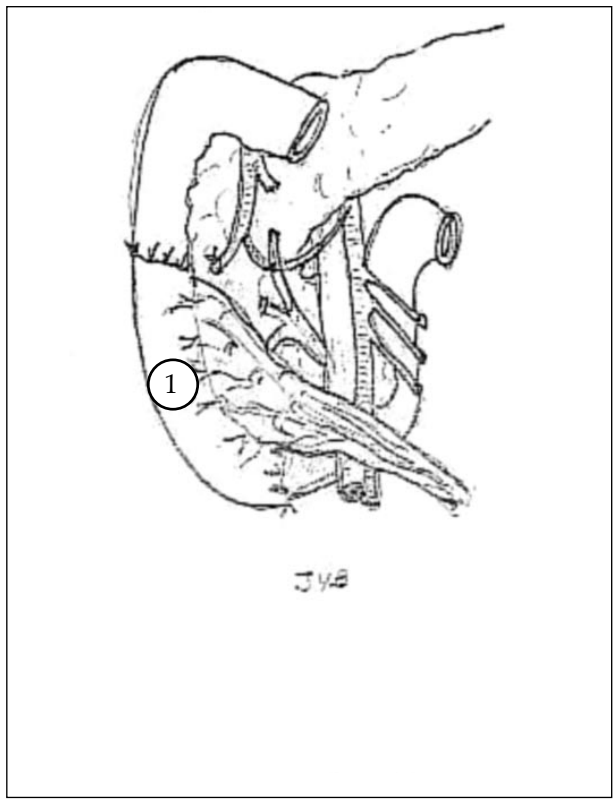

Fig. 2 D: Reconstruction of duodenum with the ileal loop
1 = Pedicled ileal loop

Fig 2(a-d): Procedure steps of case number 2

catheter in the common bile duct was removed and a cholecystectomy performed. One suction drain was put behind the head of the pancreas. The operative time was 180 minutes. The postoperative period was uneventful. He was started on fluids on the fourth postoperative day and returned to normal diet after six days. He was discharged from the hospital after 15 days. Pathology revealed a 6 cm segment of duodenum with a tumor measuring 3 x 3 x 2.5 cm located at the submucosa and muscularis mucosa of the duodenal wall. The tumor was located at 1.5 cm from the proximal margin and 1.6 cm from the distal one. The nodular mass did not invade the serosal layer. After imatinib therapy, the residual GIST (T< 5 cm, 4 mitosis per 50 hpf) showed no area of necrosis or lymphovascular invasion. CD34 was negative and Ki67 showed low positivity. Patient stopped imatinib after the surgery. The last upper GI endoscopy and abdomen-pelvis CT scan performed on the 20th January 2008, showed no recurrence.

DISCUSSION

For surgical resection of neoplasms of duodenum there are several options. Pancreaticoduodenectomy has been advocated for adenocarcinoma and carcinoids[1,2]. But in carefully selected group of patients with GIST, severe dysplasia, adenomas and micro-invasive adenocarcinomas, cure can be achieved by duodenal resection alone, if free margins can be achieved.

In these cases, pancreaticoduodenectomy may be an excessive procedure, if there is no infiltration of the pancreatic head or surrounding tissues by the tumor. But even in these cases, pancreaticoduodenectomy must be performed when there is infiltration of the head of pancreas, or if, the head of pancreas is not healthy (inflammation), duodenectomy is not radical or peripancreatic tissues are encroached by tumors[2,3]. For small GIST's opposite the mesenteric portion, resection with primary closure of the duodenum can be performed. Goh *et al*[4] described a new technique for local resection of GIST when the tumor involves the mesenteric aspect of second part of duodenum to avoid pancreaticoduodenectomy. To ensure biliary drainage, they performed a Roux-en-Y choledocojejunostomy since the ampulla of Vater was close to the edge of the defect that would probably be injured by suturing. The duodenum was repaired by displacing the remnant common bile duct as a patch to cover the defect.

Duodenectomy is a difficult surgical procedure. It requires a good anatomical knowledge of the head of pancreas and a surgeon experienced in pancreatic surgery[5,6]. Total or partial duodenectomy preserving the pancreatic head needs a very cautious dissection because the mesenteric duodenal wall is always very thin and can be injured easily. Bleeding due to multiple small vessels must be controlled carefully to avoid hemorrhage. Frozen sections on the margins of the specimen must be free of the disease. The main problem is to rebuild the defect after duodenectomy and it is ofcourse more complicated when the papilla of Vater must be removed with the second duodenum. For Cases 1 and 2, the papilla of Vater could be preserved. We rebuilt the duodenal defect with a pedicled ileal loop. The papilla of Vater was fixed to the posterior ileal wall. This technique was easy to perform and was successful. It seems less complicated than other techniques, mainly with Roux-en-Y choledocojejunostomy proposed in the literature[5, 6].

If the papilla of Vater must be removed with the duodenum, the technique described by Gertsch and Blumgart[7] must be considered. After duodenectomy and resection of the ampulla of Vater, the common bile duct and the pancreatic duct are sutured together and fixed to the posterior ileal loop wall. Drainage of the common bile duct is not necessary but cholecystectomy must be performed with intraoperative cholangiography so as to define the anatomy. Gertsch and Blumgart also stressed that leaving the gall bladder in place after resection of the papilla is contraindicated because of the risk of cholecystitis[7]. Duodenopancreatectomy must be performed in all the cases when free margins cannot be achieved for severe dysplasia, adenomas, or GIST's.

Post operative complications could be hemorrhage or large hematoma around the pancreatic head due to bleeding of the small vessels coming from the pancreas or pancreatic fistula due to accessory pancreatic ducts. So during the dissection of the mesenteric duodenal portion, careful hemostasis of all the small vessels must be performed and all accessory pancreatic ducts must be recognized and tied.

A careful follow up of patients operated for duodenal neoplasm must be performed. According to Miettental *et al*[8] 86% of the duodenal GIST patients will die of the disease, if the tumor was > 5 cm with more than 5 mitosis per 50 hpf. No recurrence or metastases were seen in patients with tumor less than 2 cm with less than 5 mitosis per 50 hpf[8,9]. But for Case 2, patients with intermediate risk occasionally develop metastasis or local recurrence. For them a long term follow up is strongly advisable. As far as severe dysplasia with or without adenoma is concerned the long term outcome remains unpredictable[10-12]. Duodenopancreatectomy must be performed when severe dysplasia and/or adenoma recurred to prevent adenocarcinoma.

CONCLUSION

Duodenectomy alone instead of the radical pancreaticoduodenectomy is a safer surgical procedure which can be applied to carefully selected group of patients who have GIST or non- invasive epithelial tumor of the duodenum.

Invited Commentary

There have been some sporadic case reports in the literature of pancreas-sparing duodenectomy. Although claims of less aggressive surgery (compared to pancreaticoduodenectomy) and survival benefits on the short term has been made, the fact remains that these surgeries suffer from being less optimal and are a breach of radical oncologic principles in operating on malignant and marginally malignant lesions. GIST are very slowly growing tumors and recurrence and metastasis are seen after more than five or ten years. The last one I managed was a case who showed liver metastasis more than 15 years after radical excision of the primary lesion despite annual follow up and repeated CT scans.

Reporting such limited experience and short follow-up, would not justify their routine use. In the absence of systematic or randomized studies by comparing these procedures to the well-established procedure of pancreatoduodenectomy, one should be very cautious in advocating these techniques.

The fact that a procedure can be performed does not necessarily entail that we should perform it. In suspicious or malignant tumors no procedure short of radical surgery should be acceptable.

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Erratum

Kuwait Medical Journal 2010; 42 (2) Front cover contents list error

REVIEW ARTICLE

Cell Mediated Immunity Assays Identify Proteins of Diagnostic and Vaccine Potential from Genomic Regions of Difference of Mycobacterium Tuberculosis

Author: Abu Salim Mustafa

Authorship of the above review article was wrongly listed as Houda I Nashawi, Mona A Ghazal, and Samuel B Kombian in the front cover contents page while the author was Abu Salim Mustafa. The author name given in the article published: 2010; 42(2):98 is confirmed as correct.
The Publisher regrets this error.

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2010, 42 (3): 249-251

Prevalence of Helicobacter Pylori Infection among New Outpatients with Dyspepsia in Kuwait

Alazmi WM, Siddique I, Alateeqi N, Al-Nakib B
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BMC Gastroenterol 2010; 10:14

Background: Testing and treatment for Helicobacter pylori has become widely accepted as the approach of choice for patients with chronic dyspepsia but no alarming features. We evaluated H. pylori status among outpatients with uninvestigated dyspepsia in Kuwait.
Methods: A prospectively collected database for 1035 patients who had undergone 13C-urea breath tests (UBT) for various indications was reviewed for the period from October 2007 to July 2009. The status of H. pylori in dyspeptic patients was determined by UBT.
Results: Among the 362 patients who had undergone UBT for uninvestigated dyspepsia, 49.7% were positive for H. pylori (95% CI = 44%-55%) and the percentage increased with age (35.8% at 20 - 29 years, 95% CI = 25.4% - 47.2%; 59.3% at 30 - 39 years, 95% CI = 48.5% - 69.5%) (P = 0.013). The prevalence of H. pylori was 42.6% among Kuwaitis (95% CI = 35%-50%) and 57.6% (95% CI = 49.8%-65%) among expatriates (p = 0.004). The prevalence among males was 51.3%, while in females it was 48.6%.
Conclusions: Almost half of the patients with dyspeptic symptoms in Kuwait were positive for H. pylori, though the prevalence varied with age and was higher among expatriates. The American Gastroenterology Association guidelines recommending testing and treatment for H. pylori for patients with uninvestigated dyspepsia should be endorsed in Kuwait.

Genetic Affinities of Helicobacter Pylori Isolates from Ethnic Arabs in Kuwait

Albert MJ, Al-Akbal HM, Dhar R, De R, Mukhopadhyay AK

Gut Pathog 2010; 2:6

Helicobacter pylori is one of the most genetically diverse of bacterial species, and since the 5'-end of cagA gene and the middle allele of vacA gene of H. pylori from different populations exhibit considerable polymorphisms, these sequence diversities were used to gain insights into the genetic affinities of this gastric pathogen from different populations. Because the genetic affinity of Arab strains from the Arabian Gulf is not known, we carried out genetic analysis based on sequence diversities of the cagA and the vacA genes of H. pylori from 9 ethnic Arabs in Kuwait. The analysis showed that the Kuwaiti isolates are closely related to the Indo-European group of strains, although some strains have a tendency to form a separate cluster close to the Indo- European group, but clearly distinct from East Asian strains. However, these results need to be confirmed by analyses of neutral markers (house-keeping genes in a multi-locus sequence typing [MLST]) platform. The profiling of virulence-associated genes may have resulted from ecologically distinct populations due to human migration and geographical separation over long periods of time.

Assessment of Metabolic Response to Pre-operative Treatment of Rectal Cancer

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Gulf J Oncolog 2010; 1:59-66

In the era of targeted therapy and high precision radiotherapy for patients with cancer, tailoring and individualization of treatment is needed more and more. In part to avoid ineffective administration of a toxic treatment to a patient that unlikely to get any benefit of it. And also to decrease the expenses of treatment and saving the drugs and resources to patients that deserve. Many predictive factors and markers are searched and well-known in many malignancies, but still rectal cancer lacks such predictors. As the pre-operative chemoradiotherapy is becoming the standard of care of treating patients with locally advanced rectal carcinoma, a predictive factor, or at least an early indicator, of patient's response to treatment is needed. First, it may help to modulate the pre-operative treatment by employing another chemotherapeutic or targeted agent e.g. oxaloplatin or cetuximab instead of the standard fluorouracil compounds. It may also help to avoid continuation of unnecessary protracted course of radiotherapy for 5 - 6 weeks for a patient who is unlikely to achieve a satisfactory response. This will help to avoid the definite toxicity of pelvic irradiation and avoid wasting time before going to surgery. Here comes the role of imaging techniques in predicting the metabolic response such as functional computerized tomography (CT) and magnetic resonance imaging (MRI) or positron-emission tomography (PET) scan. In this review we will go through the principles, indications and benefits of employing such techniques in the assessment of response to pre-operative chemoradiotherapy of rectal cancer.
Keywords: Rectal cancer, chemoradiotherapy, metabolic response, predictor.

Cancer in Kuwait: Magnitude of the Problem

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Gulf J Oncolog 2010; 1:7-14

Cancer registry data obtained from the Kuwait Cancer Registry at Kuwait Cancer Control Center (KCCC) of Ministry of Health, State of Kuwait. The data covers the years 1974 to 2007.
Aim of this study: was to estimate the magnitude of the cancer problem in Kuwait over the period 1974-2007.
Materials and methods: Age-adjusted incidence rates (ASR) with standard error (er) and 95% confidence intervals (95% CI) of age-standardized rates were estimated. Statistical significance was assessed by examining the standardized rate ratio (SRR).
Results: It was noted that by following the Cancer registry data there was a trend of increase in adjusted rates among both males and females. Looking into specific cancers it was noticed that comparing the ASR of colorectal cancer among Kuwaiti males, it increased by about 5 folds over the last 33 years and ranked the 1st most frequent site on the years 2003-2007. Prostate cancer incidence increased by 3 folds (14.5 cases /100,000 populations) and ranked the 4th most frequent site among Kuwaiti males. The incidence of Non Hodgkin's Lymphoma (NHL) and leukemia had increased by 1.5 to 2 folds over the same time period. The rise of lung cancer incidence declined to similar rates compared to that observed in the early 70s and 80s. For Kuwaiti females breast cancer had the highest incidence among Kuwaiti population (15 cases /100,000 populations), it increased by 3 folds (50 cases /100,000 populations) over the last 33 years. The incidence of colorectal cancer increased by about 4 folds; (13 cases /100,000 populations). NHL and

leukemia increased by 2 - 2.5 folds over the same studied duration. Meanwhile Thyroid cancer increased by one fold.

Conclusion and Recommendations: Some of the differences in cancer rates over the last 33 years are likely to be attributable to the variation in exposure to specific etiologic factors that are caused by differences in lifestyle and habits, such as dietary, physical activity and obesity. Further research with a view to understanding these changes in cancer incidence is warranted. The need for an interventional prevention programs that vigorously involve, diet, anti-smoking and physical activity among both sexes.

Developing a National Physical Activity Plan: the Kuwait Example

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Glob Health Promot. 2010; 17:52-57

A rapid increase in economic well-being and urbanization in Kuwait have been accompanied by profound changes in lifestyle, including low levels of physical activity in all population groups. These changes have contributed to a high prevalence of overweight and obesity and to the escalation of the non-communicable disease rates, particularly coronary heart disease, stroke, hypertension and diabetes. The evolution of physical activity promotion, internationally, and a series of related meetings in Kuwait and neighboring countries, have started to generate an awareness among health authorities of the importance of physical activity in health promotion and disease prevention. A National Physical Activity Committee has been formed to design and implement a National Physical Activity Plan, which could also serve as a model for other countries. The authors describe the background and principles behind the development of the National Plan, summarize a template based upon the Kuwait experience and share the lessons learned from these efforts.

Butyrylcholinesterase Activity in Women with Diabetes Mellitus in Pregnancy: Correlation with Antioxidant Activity

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J Obstet Gynaecol 2010; 30:122-126

A total of: 25 women with gestational diabetes, 25 with type 2 diabetes, 21 with healthy pregnancies and 15 non-pregnant healthy controls were investigated to evaluate the relationship between butyrylcholinesterase activity and antioxidant status in the serum and placenta of diabetic pregnant women. Levels of antioxidant activities were estimated by Randox Kits and malondialdehyde and butyrylcholinesterase by colorimetric methods. Butyrylcholinesterase activity was elevated in the serum and placenta in normal pregnancy vs diabetic cohorts ($p < 0.01$) and there was a higher activity level in gestational and type 2 diabetes on insulin ($p < 0.05$) compared with diet controlled. There was higher malondialdehyde and lower antioxidant activity in diet vs insulin controlled diabetes ($p < 0.01$). Serum and placental butyrylcholinesterase activity showed a strong inverse correlation with malondialdehyde ($r = -0.876$, $p < 0.001$) and ($r = 0.542$, $p < 0.01$), but strong positive correlation with total antioxidant activity in serum ($r = 0.764$, $p < 0.001$) and placenta ($r = 0.642$, $p < 0.01$). Butyrylcholinesterase may therefore, be involved in reducing oxidative stress in diabetic pregnancy.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2010; 42 (2): 252-261

28th World Congress of **Endourology**
Sep 01 - 04, 2010
Chicago, IL, *United States*
Contact: Bailey-Turner Chernise
E-Mail: cturner@bsdad.uchicago.edu

Society of **Laparoendoscopic** Surgeons: 19th SLS Annual Meeting and Endo Expo 2010
Sept 01- 04, 2010
New York, NY, *United States*
Contact: SLS Secretariat
Phone: 1-800-446-2659 / 1-305-665-9959; Fax: 1-305-667-4123
E-Mail: conferences@sls.org

World **Psychiatric** Association 2010 Regional Meeting
Sept 01 - 05, 2010
Beijing, *China*
Contact: Dr. Yizhuang Zou
E-Mail: yzouy@263.net

33rd Annual Meeting of the European Academy of Facial **Plastic Surgery**
Sep 01 - 05, 2010
Antalya, *Turkey*
Contact: Prof. Fazil Apaydin
Phone: 90-216-449-4945 Fax: 90-216-449-6410
E-Mail: eafps2010@k2-events.com

Breast Imaging: A Comprehensive Review Meeting
Sep 02 - 04, 2010
Bruges, *Belgium*
Contact: Meeting Organiser: King Conventions
Phone: 00-32-9-235-2295; Fax: 00-32-9-233-8597
E-Mail: breast@kingconventions.be

45th Annual Meeting American Society of **Head and Neck Radiology** (ASHNR)
Sep 07- 11, 2011
San Diego, CA, *United States*
Contact: Meeting Organiser: ASHNR, 2210 Midwest Road, Suite 207 Oak Brook, Illinois 60523-8205
Phone: 630-574-0220; Fax: 630-574-0661

2010 World **Molecular Imaging** Congress
Sep 08 - 11, 2010
Kyoto, *Japan*
Contact: Nichole Navar
Phone: 310-215-9730; Fax: 310-215-9731
E-Mail: ami@ami-imaging.org

The XXIX Annual European Society for **Regional Anaesthesia** Congress (ESRA 2010)
Sep 08 - 11, 2010
Porto, *Portugal*
Contact: Secretariat: KENES International
Phone: 41-228-070-360; Fax: 41-223-280-724
E-Mail: esra2010@kenes.com

28th ESOPRS Annual Meeting - European Society of **Ophthalmic Plastic** and **Reconstructive Surgery**
Sep 09 - 11, 2010
Munich, Germany
Contact: Frau Claudia Schäfer
Phone: 0049-0-89-307-1011; Fax: 0049-0-89-307-1021
E-Mail: claudia.schaefer@cocs.de

40th Annual Meeting of the European Society for **Dermatological Research** (ESDR)
Sep 09 - 11, 2010
Helsinki, *Finland*
Contact: ESDR Secretariat
Phone: 41-22-321-4890; Fax: 41-22-321-4892

European Society of **Urogenital Radiology: 2010** Symposium of the ESUR
Sep 09 - 12, 2010
City: Bruges, *Belgium*
Contact: ESUR Head Office
Phone: 43-15-334-064; Fax: 43-15-334-064 - 448
E-Mail: ESURSecretary@ecr.org

AAO-HNSF Annual Meeting & **Oto** Expo 2011
Sep 11- 14, 2011
San Francisco, CA, *United States*
Contact: Meeting Organiser: AAO-HNSF, 1650 Diagonal Road, Alexandria, VA 22314-2857, USA
Phone: 1-703-836-4444; Fax: 1-703-519-1546
E-Mail: meetings@entnet.org

XVIIth International Congress of **Neuropathology**
Sep 11- 15, 2010
Salzburg, *Austria*
Brigitte Millán-Ruiz
Phone: 43-1-404-005-573; Fax: 43-1-404-005-511
E-Mail: brigitte.millan-ruiz@meduniwien.ac.at

24th European Association for **Cardio-Thoracic Surgery** (EACTS) Annual Meeting 2010
Sep 11- 15, 2010
Geneva, *Switzerland*
Contact: Meeting Organiser
Phone: 44-0-1753-832-166; Fax: 44-0-1753-620-407
E-Mail: info@eacts.co.uk

ITC 2010: The 14th International **Thyroid** Congress
Sep 11 - 16, 2010
Paris, *France*
Contact: Conference Secretariat
Phone: 0-153-858-280; Fax: 0-153-858-283
E-Mail: itc2010info@mci-group.com

39th Annual Meeting of the American College of **Clinical Pharmacology**
Sep 12 - 14, 2010
Baltimore, MD, *United States*
Contact: American College of Clinical Pharmacology, 3 Ellinwood Court, New Hartford, NY 13413-1105
Phone: 315-768-6117; Fax: 315-768-6119
E-Mail: linda@accp1.org, tami@accp1.org

International Federation of Fertility Societies (IFFS): 20th World Congress on **Fertility & Sterility**
Sept 12 - 15, 2010
Munich, *Germany*
Contact: INTERPLAN Congress, Meeting & Event Management AG Office
Phone: 49-8-954-823-473; Fax: 49-8-954-823-442
E-Mail: f.rama@interplan.de

38th Annual Meeting of the International Society **for Pediatric Neurosurgery**
Sept 13 - 16, 2010
Jeju, *Korea*
Contact: Gordon Mccomb
E-Mail: gmcomb@chla.usc.edu

11th Congress on **Reproductive Biomedicine** & 6th Congress on **Stem Cell Biology** & Technology
Sep 15 - 17, 2010
Middle East, *Iran*
Contact: A Orae
Phone: 098-21-2231-0406; Fax: 098-21-2231-0406
E-Mail: royancongress@gmail.com

15th Congress of the European Society of **Surgical Oncology** (ESSO)
Sep15 - 17, 2010
Bordeaux, *France*
Contact: Congress Secretariat
Phone: 32-0-2-775-0201; Fax: 32-0-2-775-0200
E-Mail: ESSO2010@ecco-org.eu

The First International Congress of **Regional Anesthesia and Pain Interventions**
Sep 15- 17, 2010
Tehran, *Iran*
Contact: Dr Farnad Imani
Phone: 9821-6651-5758; Fax: 9821-6655-0138
E-Mail: info@israpm2010.ir

2010 European **Respiratory** Society (ERS) Annual Congress
Sep 18 - 22, 2010
Barcelona, *Spain*
Contact: Conference Secretariat: ERS 2010 c/o K.I.T. Group GmbH
Phone: 49-0-30-246-032-20 Fax: 49-0-30-246-032-00
E-Mail: ers2010registration@kit-group.org

Fetal and **Women's** Imaging 2010
Sep 19 - 21, 2010
Seattle, WA, *United States*
Contact: World Class CME
Phone: 803-802-1300; Fax: 803-802-1335
E-Mail:office@worldclasscme.com

World Congress on **Refractive Error**
Sep 20 - 22, 2010
Durban, *South Africa*
Contact: Conference Secretariat
Phone: 27-31-201-1470; Fax: 27-31-201-1510
E-Mail: events@confcall.co.za

Trans catheter Cardiovascular Therapeutics (TCT) Conference 2010
Sep21- 25, 2010
Washington, DC, *United States*
Contact: Conference Secretariat
Phone: 866-695-5498 or 001-514-228-3034; Fax: 514-228-3073
E-Mail: TCT@laser-registration.com

Central European Congress of **Rheumatology** (CECR2010)
Sep 22 - 24, 2010
Sopron, *Hungary*
Contact: Prof Gyula Poór
Phone: 36-1-336-0464
E-Mail: titkarsag@mre.hu

40th Annual Meeting of the German Society of **Immunology**
Sep 22- 25, 2010
Leipzig, *Germany*
Contact: Nadia Al-Hamadi
Phone: 49-0-3641-3533-2236; Fax: 49-0-3641-3533-22309
E-Mail: immunologie2010@conventus.de

ESPE 2010: 49th Annual Meeting of the European Society for **Pediatric Endocrinology**
Sep 22 - 25, 2010
Prague, *Czech Republic*
Contact: Congress Secretariat
Phone: 46-0-8-459-66-00; Fax: 46-0-8-661-91-25
E-Mail: espe2010@congrex.com

12th International Congress of **Cardiothoracic and Vascular Anesthesia**
Sep 22- 24, 2010
Beijing, *China*
Contact: Conference Secretariat
Phone: 86-10-8515-8150 or 86-10-8515-8473; Fax: 86-10-6512-3754
E-Mail: iccva2010@gmail.com

The 13th Annual International Congress of **Pediatric Hepatology, Gastroenterology and Nutrition**
Sep 22- 25, 2010
Sharm-El Sheikh, Egypt
Contact: Mortada El-Shabrawi
Phone: 201-2313-3705; Fax: 202-3761-9012
E-Mail: melshabrawi@medicine.cu.edu.eg

American Academy of **Otolaryngic Allergy** Annual Meeting (AAOA) 2010
Sep 23 - 25, 2010
Boston, MA, *United States*
Contact: Meeting Organiser
Phone: 202-955-5010; Fax: 202-955-5016
E-Mail: info@aaoaf.com

The 1st World Congress on Controversies in **Gastroenterology & Liver Diseases** (C-GOLD)
Sep 23 - 26, 2010
Prague, *Czech Republic*
Contact: Ilana
Phone: 972-3-566-6166; Fax: 972-3-566-6177
E-Mail:cgold@comtecmed.com

ASNC2010: 15th Annual Scientific Session of the American Society of **Nuclear Cardiology**
Sep 23 - 26, 2010
Philadelphia, PA, United States
Contact: American Society of Nuclear Cardiology
Phone301-215- 7575; Fax: 301-215-7113
E-Mail: asnc2010@asnc.org

19th EUROCHAP 2010 European Chapter Congress of the International Union of **Angiology**
Sep 24 - 26, 2010
Paris, *France*
Contact: Conference Secretariat
Phone: 33-0-140-783-800; Fax: 33-0-140-783-801
E-Mail: info@aimfrance.fr

11th International Conference on **Alzheimer's** Drug Discovery
Sep 26 - 28, 2010
Jersey City, NJ, *United States*
Contact: Conference Secretariat
Phone: 1-773-784-8134
E-Mail: meetings@worldeventsforum.com

23rd Scientific Meeting of the International Society of **Hypertension**
Sep 26 - 30, 2010
Vancouver, BC, Canada
Contact: Sandy Becker
Phone: 1-604-984-6448; Fax: 1-604-984-6434
E-Mail: info@vancouverhypertension2010.com

7th Annual Conference of the German Joint Society for **Clinical Chemistry and Laboratory Medicine** (DGKL)
Sep 29 - Oct 02, 2010
Mannheim, Germany
Contact: Oliver Ong
Phone: 49-0-3641-3533-22-301; Fax: 49-0-3641-3533-21
E-Mail: dgkl2010@conventus.de

Mayo Clinic **Stroke and Cerebrovascular Disease** Review
October 01 - 03, 2010
Amelia Island, FL, *United States*
Contact: Linda Gibson
Phone: 800-462-9633; Fax: 904-953-2954
E-Mail: cme-jax@mayo.edu

Australian Society of **Anaesthetists** National Scientific Congress 2010
Oct 02- 05, 2010
Melbourne, *Australia*
Contact: Congress Secretariat
Phone: 61-3-9682-0500; Fax: 61-3-9682-0344
E-Mail: info@asa2010.com or registration@asa2010.com

Cardiovascular and Interventional Radiological Society of Europe (CIRSE 2010) Annual Congress
Oct 02 - 06, 2010
Valencia, *Spain*
Contact: Secretariat - CIRSE
E-Mail: info@cirse.com

American College of **Surgeons** 96th Annual Meeting
Oct 03- 07, 2010
Washington, DC, *United States*
Contact: American College of Surgeons
Phone: 312-202-5000; Fax: 312-202-5001
E-Mail: postmaster@facs.org

XVIIIth World Congress on **Psychiatric Genetics**
Oct 03 - 07, 2010
Athens, *Greece*
Contact: Mrs Penelope Mitrogianni
Phone: 30-210-725-7693; Fax: 30-210-725-7532
E-Mail: info@ispg2010.org

18th International Congress on **Palliative Care**
Oct 05- 08, 2010
City: Montreal, QC, *Canada*
Contact: Frank Salvatori
Phone: 450-292-3456 ext 224; Fax: 450-292-3453
E-Mail: frank@odon.ca

International **Diabetes** Summit
Oct 05 - 06, 2010
Dubai, *United Arab Emirates*
Contact: Lucia Kasanicka
Phone: 9181-0580-5411; Fax: 9180-4050-9933
E-Mail: lucia.kasanicka@fleminggulf.com

WINFOCUS 2010: 6th World Congress on **Ultrasound in Emergency & Critical Care Medicine**
Oct 06 - 09, 2010
Rome, *Italy*
Contact: Winfocus Secretariat
Phone: 39-051-230-385; Fax: 39-051-221-894
E-Mail: secretariat@winfocus.org

19th Congress of the European Academy of **Dermatology and Venereology** (EADV)
Oct 06 - 10, 2010
Gothenburg, *Sweden*
Contact: EADV Office
Phone: 322-650-0090; Fax: 322-650-0098
E-Mail: office@eadv.org

XII National Congress of **Cardiology**
Oct 07- 10, 2010
Albena,Varna, *Bulgaria*
Contact: Maria Nedialkova
Phone: 359-2-988-8035; Fax: 359-2-980-6074
E-Mail: cim@cim.bg or maria@cim.bg

MASCON 2010
Oct 08 - 10, 2010
Mumbai, *India*
Contact: Dr.Vijay Shetty or Dr.Mayuri Shetty
Phone: 0-982-107-6279 or 0-982-018-5527; Fax: 91-22-2590-6346
E-Mail: info@mumbaiana.org

26th Annual **Echocardiography in Pediatric and Adult Congenital Heart Disease** Symposium
Oct 10 - 13, 2010
Rochester, MN, *United States*
Contact: Conference Secretariat
Phone: 800-323-2688
E-Mail: cme@mayo.edu

Breast MRI: Science, Technique, and Interpretation, Including Clinical Correlation and Recent Developments
Oct 14 - 17, 2010
Cincinnati, OH, *United States*
Contact: Beth Smith
Phone: 513-924-5365; Fax: 513-352-9424
E-Mail: bethsmith@proscan.com

EMAA 2010 - European Masters in **Aesthetic & Anti-Aging Medicine**
Oct 15 - 17, 2010
Paris, *France*
Contact: Christophe Luino
Phone: 01-56-837-800; Fax: 01-56-837-805
E-Mail: contact@euromedicom.com

Laser and **Esthetic Therapy** in Ethnic Skin (LETES)
Oct 16 - 17, 2010
Riyadh, *Saudi Arabia*
Contact: Samaa Hassan
Phone: 966-1-467-1551 or 966-1-467-1556 ext 26 Fax: 966-1-469-9110
E-Mail: info@letes.net

2010 Annual Meeting of the American Academy of **Ophthalmology**
Oct 16 - 19, 2010
Chicago, IL, *United States*
Contact: American Academy of Ophthalmology
Phone: 415-447-0320
E-Mail: meetings@aao.org

The 7th Combined Meeting of **Orthopaedic** Research Societies
Oct 16 - 20, 2010
Kyoto, *Japan*
Contact: Secretariat
Fax: 81-52-950-6146
E-Mail: cors2010@cs-oto.com

ASA 2010: **American Society of Anesthesiologists** Annual Meeting
Oct 16 - 20, 2010
San Diego, CA, *United States*
Contact: Meeting Organiser
E-Mail: annmtg@asahq.org

Acute Cardiac Care 2010
Oct 16 - 19, 2010
Copenhagen, *Denmark*
Contact: Secretariat - Acute Cardiac Care
Phone: 33-4-92-94-76-00; Fax: 33-4-92-94-76-01

20th World Congress of the **IASGO**
Oct 20 - 23, 2010
Cairo, *Egypt*
Contact: Dr. Shahenda El Hawary
Phone: 20-233-023-642; Fax: 20-233-027-672
E-Mail:cobshahi@link.net

19th Regional Conference of **Dermatology** (Asian-Australasian) incorporating 2nd Annual Meeting of Asian Academy of **Dermatology & Venereology**/ 35th Annual Meeting of Dermatological Society of Malaysia
Oct 20- 23, 2010
Kota Kinabalu, *Malaysia*
Contact: Ms Molly Kong
Phone: 603-4023-4700 or 603-4023-4025; Fax: 603-4023-8100
E-Mail: secretariat@asianderm.org

Turkish **Respiratory** Society 32nd Annual Congress
Oct 20 - 24, 2010
City: Antalya, *Turkey*
Contact: Erdinc Tan
Phone: 902-164-494-945; Fax: 902-164-494-945
E-Mail: solunum2010@k2-events.com

Lymphoma & Myeloma 2010: An International Congress on **Hematologic Malignancies**
Oct 21- 23, 2010
New York, NY, *United States*
Contact: Imedex Customer Service
Phone: 1-678-242-0906; Fax: 1-678-242-0920
E-Mail: meetings@imedex.com

6th International Congress of the Asia-Pacific **Metabolic and Bariatric Surgical** Society
Oct 21- 23, 2010
Singapore, *Singapore*
Contact: Mrs Norizam
Phone: 656-772-2920; Fax: 656-774-6077
E-Mail: info@apmbss2010.com

2010 ASDS (American Society for **Dermatologic Surgery**) Annual Meeting
Oct 21- 24, 2010
Chicago, IL, *United States*
Contact: American Society for Dermatologic Surgery
Phone: 847-956-0900

48th Annual Meeting of the **Infectious Diseases** Society of America
Oct 21- 24, 2010
Vancouver, BC, *Canada*
Contact: IDSA, 1300 Wilson Blvd, Suite 300, Arlington, VA 22209
Phone: 703-299-0200; Fax: 703-299-0204
E-Mail: info@idsociety.org

42nd Danube Symposium for **Neurological Sciences and Continuing Education** with International Participation
Oct 21 - 24, 2010
Zagreb, *Croatia*
Contact: Mr. Branimir Pavlin
Phone: 385-1-484-7604; Fax: 385-1-484-7606
E-Mail: top-tours@zg.t-com.hr

26th National Turkish **Cardiology** Congress 2010
Oct 21- 24, 2010
Istanbul, *Turkey*
Contact: Ilkay Gucuk
Phone: 0090-212-282-9232; Fax: 0090-212-268-1841
E-Mail: ilkay.gucuk@globalturizm.com.tr

American Society for **Reproductive Medicine 66th Annual Meeting**
Oct 23 - 27, 2010
Denver, CO, *United States*
Contact: American Society for Reproductive Medicine, 1209 Montgomery Highway, Birmingham, Alabama 35216-2809
Phone: 205-978-5000; Fax: 205-978-5005
E-Mail: asrm@asrm.org

2nd International **Pain Symposium**
Oct 26 - 28, 2010
Riyadh, *Saudi Arabia*
Secretariat: Academic and Training Affairs, CME Section, P O Box 354, Riyadh 11211, MBC 36, Saudi Arabia
Phone: 00-966-1442-7238; Fax: 00-966-1442-4153
E-Mail: web-symposia@kfshrc.edu.sa

2nd Annual Congress of the Global **Diabetes** Alliance
Oct 26 - 29, 2010
Cairo, *Egypt*
Contact: Mahmoud Ibrahim
Phone: 2012-213-1868 or 2010-657-0064; Fax: 202-2671-8421
E-Mail: mahmoud@global-diabetes.org

The American Academy of **Child and Adolescent Psychiatry** 57th Annual Meeting
Oct 26 - 31, 2010
New York, NY,*United States*
Contact: The American Academy of Child and Adolescent Psychiatry 3615 Wisconsin Avenue, N.W, Washington, D.C.20016-3007
Phone: 202-966-7300; Fax: 202-966-2891
E-Mail: meetings@aacap.org

36th International Society of **Pediatric and Adolescent Diabetes** (ISPAD) Annual Meeting 2010
Oct 27 - 30, 2010
Buenos Aires, *Argentina*
Contact: ISPAD 2010 Conference Secretariat
Phone: 49-30-246-03-210; Fax: 49-30-246-03-200
E-Mail: ispad2010@kit-group.org

32nd Turkish National Congress of **Otorhinolaryngology and Head & Neck Surgery**
Oct 27- 31, 2010
Antalya, *Turkey*
Contact: Prof. Atilla Tekat
Phone: 90-216-449-4945 Fax: 90-216-449-6410
E-Mail: kbb2010@k2-events.com

2010 American Society of **Clincial Pathology** (ASCP) Annual Meeting
Oct 27 - 31, 2010
San Francisco, CA, *United States*
Contact: Meeting Organiser
Phone: 800-267-2727 Fax: 312-541-4472
E-Mail: info@ascp.org

DROP3 (Debrecen Rheumatology Program): **Vascular Rheumatology** and **Immunology**
Oct 28 - 31, 2010
Debrecen, *Hungary*
Contact: Prof Dr Zoltán Szekanecz
Phone: 36-52-255-091; Fax: 36-52-255-091
E-Mail: szekanecz@gmail.com

14th World Society of **Pain** Clinicians Congress (WSPC 2010)
Oct 28 - 31, 2010
Beijing, *China*
Contact: KENES International
Phone: 41-229-080-488 Fax: 41-229-069-140
E-Mail: wspc@kenes.com

Chest 2010: American College of **Chest** Physicians (ACCP) Annual Meeting
Oct 30 - Nov 04, 2010
Vancouver, BC, *Canada*
Contact: Meeting Organiser
Phone: 847-498-1400 or 800-343-2227

4th Asia Pacific **Cervical Spine** Society Conference
Nov 03 - 06, 2010
Sydney, NSW, *Australia*
Contact: Conference Secretariat: DC Conferences
Phone: 612-9954-4400; Fax: 612-9954-0666
E-Mail: apcss@dcconferences.com.au

XX World Congress of **Asthma** (WCA 2010)
Nov 03 - 06, 2010
Athens, *Greece*
Contact: Irene Aretha
Phone: 30-210-321-5600; Fax: 30-210-321-9296
E-Mail: wca2010@frei.gr

5th International Symposium on **Microneurosurgical Anatomy** (5th ISMA)
Nov 04- 06, 2010
Istanbul, *Turkey*
Contact: Secretariat: Alabanda Meetings
Phone: 90-312-440-5600; Fax: 90-312-440-5597
E-Mail: isma@isma2010.org

8th Annual World Congress on **Insulin Resistance, Diabetes, and Cardiovascular** Disease
Nov 04 - 06, 2010
Los Angeles, CA, *United States*
Contact: Briana Celedon
Phone: 818-342-1889; Fax: 818-342-1538
E-Mail: metabolicinst@pacbell.net

The 1st World Congress on Controversies in **Plastic Surgery & Dermatology** (CoPLASDy)
Nov 04 - 07, 2010
Barcelona, *Spain*
Contact: Congress Secretariat
Phone: 97-235-666-166
E-Mail: coplasdy@comtecmed.com

The 8th Asia Pacific Congress of **Allergy, Asthma and Clinical Immunology**
Nov 07 - 10, 2010
Singapore, *Singapore*
Contact: Stella Chee
Phone: 65-63-795-259; Fax: 65-64-752-077
E-Mail: admin@apcaaci2010.org

Chemotherapy Foundation Symposium, **Innovative Cancer Therapy** for Tomorrow Nov 09 - 13, 2010
New York, NY, *United States*
Contact: Jaclyn Silverman
Phone: 212-866-2813; Fax: 646-215-7589
E-Mail: jaclyn.silverman@mssm.edu

FACE 2010 - **Facial Aesthetic & Cosmetic** Events
Nov 12 - 13, 2010
Marrakesh, *Morocco*
Contact: Conference Secretariat: Agence ATouT.Com
Phone: 33-0-4-4254-4260; Fax: 33-0-4-4251-0068
E-Mail: contact@face-2010.com

American College of **Allergy, Asthma & Immunology** Annual Meeting 2010
Nov 12 - 17, 2010
Phoenix, AZ, *United States*
Contact: Meeting Organiser
Phone: 847-427-1294; Fax: 847-427-1200
E-Mail: mail@acaai.org / meetings@acaai.org

10th Asian-Oceania International Congress on **Skull Base Surgery** (AOSBS) in conjunction with WFNS Skull Base Course, Asian Australasian Society of **Neurological** Surgeons (AASNS) Course and World Academy of **Neurological Surgery** (WANS) Meeting
Nov 13 - 18, 2010
Bali, *Indonesia*
Contact: Santi Anwar
Phone: 62-21-5596-0180; Fax: 62-21-5596-0179
E-Mail: aosbs2010@pharma-pro.com

Society of **Obstetrics and Gynaecology** of Nigeria(SOGON) International Conference - Abuja 2010
Nov 16 - 20, 2010
Abuja, *Nigeria*
Contact: Dr. Fred Achem
Phone: 234-9-802-290-4422
E-Mail: fachem@hotmail.com

American Society of **Nephrology**: Renal Week 2010
Nov 16 - 21, 2010
Denver, CO, *United States*
Contact: Meeting Organiser
Phone: 1-202-659-0599; Fax: 1-202-659-0709
E-Mail: email@asn-online.org

Society of **Obstetrics** and **Gynaecology** of Nigeria(SOGON) International Conference - Abuja 2010
Nov 17 - 20, 2010
Abuja, *Nigeria*
Contact: Dr. Fred Achem
Phone: 234-9-802-290-4422
E-Mail: fachem@hotmail.com

The 3rd International Conference on Fixed Combination in the Treatment of **Hypertension, Dyslipidemia and Diabetes Mellitus**
Nov 18 - 20, 2010
Brisbane, QLD, *Australia*
Contact: Ronnie Katzir
Phone: 41-0-22-5330-948; Fax: 41-0-22-5802-953
E-Mail: fixed2010@fixedcombination.com

American Society of Regional **Anesthesia and Pain Medicine** (ASRA) 2010 Annual Pain Medicine Meeting and Workshops
Nov18 - 21, 2010
Phoenix, AZ, *United States*
Contact: Meeting Organiser: American Society of Regional Anesthesia and Pain Medicine Phone: 847-825-7246
E-Mail: asra@asahq.org

Hair and Scalp Diseases in Dermatological Practice. International Course and Symposium
Nov 19 - 21, 2010
Warsaw, *Poland*
Contact: Lidia Rudnicka
Phone: 0-48-225-081- 480; Fax: 0-48-225-081-492
E-Mail: lidiarudnicka@yahoo.com

6th European Federation of National Associations of **Orthopaedic Sports Traumatology** (EFOST 2010)
Nov 25 - 27, 2010
Brussels, *Belgium*
Contact: Congress Secretariat
E-Mail: maryam.shahabpour@uzbrussel.be

Osteoporosis Conference 2010
Nov 28 - Dec 01, 2010
Liverpool, England, *United Kingdom*
Contact: Kelly Hall
Phone: 44-0-1761-473-281; Fax: 44-0-1761-471-104
E-Mail: conferences@nos.org.uk

14th Asia-Oceania Congress of **Endocrinology**
Dec 02 - 05, 2010
Kuala Lumpur, *Malaysia*
Contact: Marcus Chew
Phone: 60-321-620-566; Fax: 60-321-616-560
E-Mail: marcus@console.com.my

Excellence in **Paediatrics** 2010
Dec 02 - 04, 2010
London, England, *United Kingdom*
Contact: Malvina Nezi
Phone: 30-210-688-9164; Fax: 30-210-684-4777
E-Mail: excellence@candc-group.com

WAO International Scientific Conference - **Asthma and Co-morbid Conditions:** Expanding the Practice of Allergy for Optimal Patient Care
Dec 05 - 08, 2010
Dubai, *United Arab Emirates*
Contact: WAO Secretariat
Phone: 1-414-276-1791; Fax: 1-414-276-3349
E-Mail:WISC2010@worldallergy.org

BIT's 2nd Annual International Congress of **Cardiology**
Dec 07- 09, 2010
Shanghai, *China*
Contact: Ms. April Wang or Ms. Ruby Liu
Phone: 0086-411-8479-5469 or 0086-411-8479-9609 ext. 803; Fax: 0086-411-8479-9629
E-Mail: april@bitlifesciences.com or ruby@bitlifesciences.co

Heart, Vessels & Diabetes - The European Conference
Dec 09 - 11, 2010
Lisbon, Portugal
Contact: Mr. Fabien Duval-Alexandre
Phone: 33-0-1-3904-2424; Fax: 33-0-1-3904-2425
E-Mail: hvd2010@agence-plb.com

COSMODERM XIV - The International **Aesthetic Dermatology** Congress of the European Society for **Cosmetic & Aesthetic Dermatology** (ESCAD)
Dec 09 - 12, 2010
Dresden, Germany
Contact: Isabelle Lärz
Phone: 49-3641-3533-2702; Fax: 49-3641-3533-21
E-Mail: cosmoderm2010@conventus.de

3rd **Gastroenterology and Hepatology** Post Graduate Course & 12th International Workshop on **Therapeutic Endoscopy**
Dec 10 - 13, 2010
City: Cairo, *Egypt*
Contact: Mrs. Fifi Erian
Phone: 20-2-2453-2916 or 20-2-2453-2917
Fax: 20-2-2453-3515
E-Mail: alfa@alfamedical.org

3rd Middle East Congress of **Pharmacy and Pharmaceutical Sciences** 2010
Dec 15 - 17, 2010
Sharm El-Sheik, *Egypt*
Contact: Conference Secretariat: International Conferences Company
Phone: 202-2401-7326; Fax: 202-2402-2796
E-Mail: egyicc@link.net

5th **Spine** Conference
Dec 16 - 18, 2010
Bremen, *Germany*
Contact: Mr. Justus Appelt
Phone: 49-0-3641-353-3225; Fax: 49-0-3641-353-3271
E-Mail: justus.appelt@conventus.de

American Association for **Hand Surgery** (AAHS) 41st Annual Scientific Meeting
Jan 12 - 15, 2011
Cancun, *Mexico*
Contact: Meeting Secretariat
Phone: 312-236-3307; Fax: 847-228-9436
E-Mail: contact@handsurgery.org

Maternal-Fetal Imaging 2011
Jan 23 - 25, 2011
San Antonio, TX, *United States*
Contact: World Class CME
Phone: 803-802-1300; Fax: 803-802-1335
E-Mail: office@worldclasscme.com

World **Psychiatric** Association 2011 Regional Meeting Zone 11
Jan 26 - 28, 2011
Cairo, *Egypt*
Contact: Dr. Tarek A Okasha
E-Mail: tokasha@internetegypt.com

The Society of **Thoracic Surgeons** 47th Annual Meeting
Jan 31- Feb 02, 2011
San Diego, CA, *United States*
Contact: The Society of Thoracic Surgeons, 633 N. Saint Clair Street, Suite 2320, Chicago, IL 60611
Phone: 312-202-5800 Fax: 312-202-5801
E-Mail: sts@sts.org

BC3 **Breast Cancer** Coordinated Care
Feb 03 - 05, 2011
Washington, DC, *United States*
Contact: Dennis A. Vitrella
Phone: 337-235-6606; Fax: 337-235-7300
E-Mail: DVitrella@BC3conference.com

39th National Conference of Indian Association of **Dermatologists, Venereologists** and **Leprologists** (Dermacon-2011)
Feb 03 - 06, 2011
Gurgaon, *India*
Contact: Dr. V.K. Jain
Phone: 91-98960-87888; Fax: 91-1262-213-116
E-Mail: dr_vkjain2002@yahoo.co.in

69th Annual Meeting of the American Academy of **Dermatology**
Feb 04 - 08, 2011
New Orleans, *United States*
Contact: American Academy of Dermatology
Phone: 202-842-3555 Fax: 202-842-4355

AUSTRAUMA 2011 **Trauma, Critical Care and Emergency Surgery** Conference
Feb 17 - 19, 2011
Sydney, NSW, *Australia*
Contact: Emma Thompson
Phone: 613-9276-7406; Fax: 613-9276-7431
E-Mail: austrauma@surgeons.org

American Society of **Spine Radiology** (ASSR) 2011 Annual Symposium
Feb 23 - 26, 2011
Honolulu, HI, United States
Contact: Congress Secretariat: American Society of Spine Radiology 2210 Midwest Road, Suite 207 Oak Brook, IL 60523-8205
Phone: 630-574-0220 ext. 226; Fax: 630-574-0661

9th Gulf **Heart** Association Conference
Mar 02 - 05, 2011
Muscat, *Oman*
Contact: Dr. Mohammed El Deeb
Phone: 968-2459-1444; Fax: 968-2450-2999
E-Mail: heart.oman@gmail.com

Diabetes: Caribbean CME Cruise Conference
Mar 12 - 19, 2011
Ft. Lauderdale, FL, *United States*
Contact: Martin Gerretsen MD
Phone: 1-888-647-7327; Fax: 1-888-547-7337
E-Mail: cruises@seacourses.com

Gulf **Thoracic** -2011
Mar 16 - 19, 2011
Middle East, *United Arab Emirates*
Contact: Prof. Mohamed S. Al Hajjaj MD, FRCPC
Phone: 966-50-541-9532; Fax: 966-1-248-7431
E-Mail: msalhajjaj@yahoo.com

American Association for **Thoracic Surgery** (AATS) 91st Annual Meeting 2011
May 07 - 11, 2011
Philadelphia, PA, *United States*
Contact: Meeting Organiser: American Association for Thoracic Surgery (AATS)
Phone: 978-927-8330; Fax: 978-524-8890

31st International Symposium on **Intensive Care and Emergency Medicine**
Mar 22 - 25, 2011
Brussels, *Belgium*
Contact: Véronique De Vlaeminck
Phone: 32-0-2-555-4757
E-Mail: veronique.de.vlaeminck@ulb.ac.be

2011 Annual Conference of the American Society for **Laser Medicine** and **Surgery**
Mar 30 - Apr 03, 2011
Grapevine, TX, *United States*
Contact: American Society for Laser Medicine and Surgery, 2100 Stewart Avenue, Suite 240, Wausau, WI 54401
Phone: 715-845- 9283 ; Fax: 715-848-2493
E-Mail: information@aslms.org

2011 Annual Meeting of the Royal College of **Ophthalmology**
May 24 - 26, 2011
Birmingham, England, *United Kingdom*
Contact: The Royal College of Ophthalmologists, 17 Cornwall Terrace London, NW1 4QW Phone: 44-0-2-079-350-702; Fax: 44-0-2-079-359-838
E-Mail: President@rcophth.ac.uk

American Association of **Endocrine Surgeons** (AAES) 2011 Annual Meeting
Apr 10 - 12, 2011
Houston, TX, *United States*
Contact: American Association of Endocrine Surgeons
Phone: 913-402- 7102; Fax: 913-273-9940
E-Mail: information@endocrinesurgery.org

2nd International Saudi **Critical Care** Society Conference and Annual Scientific Meeting
Apr 19 - 21, 2011
Riyadh, *Saudi Arabia*
Contact: Dr. Yasser Mandourah
Phone: 966-1-475-8022; Fax: 966-1-475-8036
E-Mail: mandourah@hotmail.com

9th International **Gastric Cancer** Congress
Apr 20 - 23, 2011
Seoul, *Republic of Korea*
Contact: Congress Secretariat: Office of 9 IGCC Fax: 82-2-837-0815
E-Mail: office@9igcc.com

10th European Symposium on **Pediatric Cochlear Implantation**
May 12 - 15, 2011
Athens, *Greece*
Contact: Secretariat: GOLDAIR Congress
Phone: 00-30-210-327-4570; Fax: 00-30-210-331-1021
E-Mail: congress@goldair.gr

Cardiology & Endocrinology: Galapagos Islands CME Cruise Conference
May 13 - 23, 2011
Galapagos Islands, *Ecuador*
Contact: Martin Gerretsen MD
Phone: 1-888-647-7327; Fax: 1-888-547-7337
E-Mail: cruises@seacourses.com

22nd European Society of **Gastrointestinal and Abdominal Radiology** (ESGAR 2011) Annual Meeting and Postgraduate Course
May 21- 24, 2011
Venise, *Italy*
Contact: Secretariat - ESGAR office
Phone: 43-1-535-89-27; Fax: 43-1-535-70-37
E-Mail:office@esgar.org

6th World Congress of the International Society of **Physical and Rehabilitation Medicine**
Jun 04 - 09, 2011
San Juan, *Puerto Rico*
Contact: Werner Van Cleemputte, Managing Director Medicongress, Waalpoel 28/34, B-9960 Assenede, Belgium
Phone: 32-0-93-443-959; Fax: 32-0-93-444-010
E-Mail: werner@medicongress.com

6th International **Pediatric Transplant** Association (IPTA) Congress on Pediatric Transplantation Jun 25 - 28, 2011
Montreal, QC, *Canada*
Contact: Congress Secretariat
Phone: 856-439-0500 ext. 4496; Fax: 856-439-0525
E-Mail: bbilofsky@ahint.com or info@IPTAonline.or

14th World Conference on **Lung Cancer**
Jul 03 - 07, 2011
Amsterdam, *Netherlands*
Contact: Grit Schoenherr
Phone: 1-604-681-2153; Fax:1-604-681-1049
E-Mail: wclc2011-marketing@icsevents.com

6th International AIDS Society (IAS) Conference on **HIV Pathogenesis, Treatment and Prevention** (IAS 2011)
Jul 17 - 20, 2011
Rome, *Italy*
Contact: Conference Secretariat: International AIDS Society
Phone: 41-0-22-7-100-800; Fax: 41-0-22-7-100-899
E-Mail: info@iasociety.org

Recent advances in **dermatology and internal medicine**
Jul 23 - Aug 10, 2011
The Arctic, *Greenland*
Contact: Dr D Czarnecki
Phone: 613-9887-0066
Fax: 613-9887-0044
E-Mail: dbczarnecki@gmail.com

2011 summer (Academy) Meeting of the American Academy of **Dermatology**
Aug 03 - 07, 2011
New York, NY, *United States*
Contact:American Academy of Dermatology
Phone: 866-503-SKIN (7546) / 847-240-1280; Fax: 847-240-1859
E-Mail: MRC@aad.org

23rd European Congress of **Pathology**
Aug 27 - Sep 01, 2011
Helsinki, *Finland*
Contact: Prof. Veli Peka Lehto
Phone: 358-9-191-26412; Fax: 358-9-191-26700
E-Mail: veli-pekka.lehto@helsinki.

45th Annual Meeting American Society of **Head and Neck Radiology** (ASHNR)
Sep 07 - 11, 2011
San Diego, CA, *United States*
Contact: Meeting Organiser: ASHNR, 2210 Midwest Road, Suite 207 Oak Brook, Illinois 60523-8205
Phone: 630-574-0220; Fax: 630-574-0661

European **Burns** Association Congress 2011
Sep 14 - 17, 2011
The Hague, *Netherlands*
Contact: Rob Zikkenheimer
Phone: 31-73-690-1415; Fax: 31-73-690-1417
E-Mail: r.zikkenheimer@congresscare.com

XVIth World Congress of **Cardiology, Echocardiography & Allied Imaging Techniques**
Sep 29 - Oct 02, 2011
Delhi, NCR, *India*
Contact: Raju Gandha
Phone: 91-124-456-300; Fax91-124-456-3100
E-Mail: worldcon2011@in.kuoni.com

ASA 2011: American Society of **Anesthesiologists** Annual Meeting
Oct 15 - 19, 2011
Chicago, IL, *United States*
Contact: Meeting Organiser
E-Mail: annmtg@asahq.org

2011 Annual Meeting of the American Academy of **Ophthalmology**
Oct 22 - 25, 2011
Orlando, FL, *United States*
Contact: American Academy of Ophthalmology
Phone: 415-447-0320
E-Mail: meetings@aao.org

American College of **Surgeons** 97th Annual Meeting
Oct 23 - 27, 2011
San Francisco, CA, *United States*
Contact: American College of Surgeons
Phone: 312-202-5000; Fax: 312-202-5001
E-Mail: postmaster@facs.org

81st Annual Meeting of the American **Thyroid** Association
Oct 26 - 30, 2011
Indian Wells, CA, *United States*
Contact: American Thyroid Association
Phone: 703-998-8890; Fax: 703-998-8893
E-Mail: thyroid@thyroid.org

WINFOCUS 2011: 7th World Congress on **Ultrasound in Emergency & Critical Care** Medicine
Nov 02 - 06, 2011
New Delhi, *India*
Contact: Winfocus Secretariat
Phone: 39-051-230-385; Fax: 39-051-221-894
E-Mail: secretariat@winfocus.org

WHO-Facts Sheet

1. Safe Food for Travellers
2. Melamine Levels in Food
3. Call for Action to Reduce the Harmful Use of Alcohol
4. WHO highlights Critical Need for Life-saving Antivenoms
5. New Who Guidance to Improve Use of Medicines for Children
6. More than Five Million People Receiving HIV Treatment

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2010, 42 (3): 262-266

1. SAFE FOOD FOR TRAVELLERS

How to avoid illnesses caused by unsafe food and drink and what to do if you get diarrhea?

Most diarrhoeal attacks are self-limited and clear up in a few days. Diarrhoea may be accompanied by nausea, vomiting and/or fever. The important thing is to avoid becoming dehydrated.

Ensure that you always drink sufficient amounts of fluids, particularly when travelling in a hot climate. This is extremely important for children. If the child is restless or irritable, or shows signs of strong thirst, or has sunken eyes, or dry skin with reduced elasticity, dehydration is already progressing and immediate medical attention should be sought.

Should bowel movements be very frequent, very watery or contain blood, or last beyond 3 days you should seek medical help. Where there is no medical help available a complete 3-day course of ciprofloxacin* (500 mg twice a day for adults, 15 mg/kg twice a day for children) can be taken.

As soon as diarrhoea starts, drink more fluids, such as oral rehydration formula, boiled, treated or bottled water, weak tea, soups or other safe fluids. Avoid any drinks that tend to remove more water from the body, including coffee, overly sweetened drinks, some medicinal teas and alcohol.

Age group Amount of fluids or ORS to drink**

- Children less than 2 years: Up to 1⁄2 cup after each loose stool
- Children 2 - 10 years: Up to 1 cup after each loose stool
- Older children and adults: Unlimited amount Contrary to common belief, medicines which reduce bowel movements are not recommended. In children, these preparations should never be used as they may cause intestinal obstruction.

* generic name - can be sold under other names

** If ORS are not available, mix 6 teaspoons of sugar plus one level teaspoon of salt in one litre of safe water ("taste of tears") and drink as indicated in the table.

Each day millions of people become ill and thousands die from a preventable foodborne disease.

The advice given here is important for every traveller, and of particular importance for high-risk groups i.e., infants and young children, pregnant women, elderly and immunocompromised individuals, including those with HIV/AIDS; persons in these groups are particularly susceptible to foodborne diseases.

Remember: Prevention is better than cure

The WHO Five Keys to Safer Food global message is adapted to specifically address the health concerns associated with travel.

Prevention of foodborne diseases: Five keys to afer food; Choose safe water and food

1. Ice cream, drinking water, ice cubes and raw milk can easily be contaminated with dangerous microorganisms or chemicals if they are made from contaminated ingredients. If in doubt, avoid them.

2. Peel all fruits and vegetables if eaten raw. Avoid those with damaged skin because toxic chemicals can be formed in damaged and mouldy foods. Green-leafed vegetables (e.g. green salads) can contain dangerous microorganisms which are difficult to remove. If in doubt about the hygienic conditions of such vegetables, avoid them.

3. If available, bottled water is the safer choice for drinking water but always check the seal to ensure

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it has not been tampered with. When the safety of drinking water is doubtful, bring it to a vigorous boil. This will kill all dangerous microorganisms present. If boiling is not possible, micropore filtering and use of disinfectant agents such as iodine tablets should be considered. Beverages which are either bottled or otherwise packaged are usually safe to drink.

4. Keep clean: Wash your hands often and always before handling and consuming food. Dangerous microorganisms are widely found in soil, water, animals and people and can be carried on hands and transferred to food. While visiting food markets, be aware of this when touching raw food and in particular raw meat, and wash hands after handling these foods. These markets often include live animals which can transmit a number of diseases including avian influenza ("bird flu"). Therefore avoid handling or close contact with these animals.

5. Raw and cooked food should be separated: When frequenting street food vendors or buffets in hotels and restaurants, make sure that cooked food is not in contact with raw food that could contaminate it. Avoid any uncooked food, apart from fruits and vegetables that can be peeled or shelled.

Dishes containing raw or undercooked eggs, such as home-made mayonnaise, some sauces and some desserts (e.g., mousse) may be dangerous. Raw food can contain dangerous microorganisms which could contaminate cooked food through direct contact. This may reintroduce disease-causing bacteria into safe, cooked food.

Before leaving home consult your physician for advice on the various diseases to which you may be exposed at your destination, and the need for vaccinations or other preventive measures. Make sure you carry in your luggage Oral Rehydration Salts (ORS), and any other medicines you may require during your travel.

The Five Keys to Safer Food global message is available at: www.who.int/foodsafety/consumer/5keys/en

2. MELAMINE LEVELS IN FOOD

New guidance to help improve food safety provided by UN food standards commission

The maximum amount of melamine allowed in powdered infant formula is 1 mg/kg and the amount of the chemical allowed in other foods and animal feed is 2.5 mg/kg, according to new rulings from the United Nations' food standards body, Codex Alimentarius Commission.

Melamine is a chemical used in a variety of industrial processes - including the manufacture of plastics used for dishware and kitchenware, and can coatings - and traces of it unavoidably get into food by contact without causing health problems, however the substance is toxic at high levels.

"Establishment of maximum levels will help governments differentiate between low levels of unavoidable melamine occurrence that do not cause health problems, and deliberate adulteration - thereby protecting public health without unnecessary impediments to international trade" said Martijn Weijtens, Chair of the Codex Committee on contaminants in foods. While not legally binding the new levels allow countries to refuse to allow the importation of products with excessive levels of melamine.

The 33rd Session of Codex Alimentarius Commission was attended by 500 delegates from about 130 countries.

Hygienic measures for safer fresh salads and seafood

Fresh, leafy vegetables are part of a healthy diet and are grown under diverse conditions and marketed both locally and globally to provide year round availability to consumers. As these products move along the supply chain from the farm to the table, they can be contaminated by pathogens such as salmonella, e. coli, and hepatitis A virus.

The new Codex measures provide specific guidance for production, harvesting, packing, processing, storage, distribution, marketing and consumer education to reduce food safety risks associated with these products. Guidance covers such aspects as the control of irrigation waters, cooling and storage and correct washing of hands by consumers.

The Commission also gave specific advice on how to control bacteria in seafood throughout the food chain. In recent years, there has been an increase in reported outbreaks of foodborne disease caused by bacterial species called Vibrio, which are typically associated with the consumption of seafood - especially oysters that are often eaten raw. The new Codex measures will help to minimize the risks.

Aflatoxins

Maximum levels of 10 micrograms/kg were set for aflatoxins in Brazil nuts (shelled, ready-to-eat) and 15 micrograms/kg for shelled Brazil nuts (intended for further processing), while the Commission also adopted a code of practice to prevent this contamination. Aflatoxins are carcinogenic fungal toxins that can contaminate corn, peanuts and other food crops such as tree nuts under certain conditions.

New methods to determine food content

The methods used for analysis and sampling are the necessary basis for food inspection and control.

The new Guidelines adopted by the Commission will make it possible to run tests to determine if foods are derived from modern biotechnology, to authenticate food varieties such as fish species and to establish the presence of allergens.

Agreement on the guidelines marks an important international consensus in the area of biotechnology where the Commission has already developed a number of guidelines related to food safety assessments for foods derived from modern biotechnology.

The 47-year-old Codex Alimentarius Commission, run jointly by Food and Agriculture Organization (FAO) and WHO, sets international food standards to protect the health of consumers and ensure fair practices in the food trade. The results of its work form the Codex Alimentarius (Latin for "food code"), a set of international food safety and quality standards. These standards, when introduced in national legislation, contribute to the safety of our foods and to international food trade.

Codex Alimentarius Commission is the longest-standing example of inter-agency cooperation in the UN system. It has 182 Member States and one Member Organization, the European Union.

For more information contact: Sari Setiogi, Media Relations Officer WHO, Geneva. Tel.: +41 22 791 3576; Mobile: +41 79 701 9467. E-mail: setiogis@who.int

3. CALL FOR ACTION TO REDUCE THE HARMFUL USE OF ALCOHOL

Countries agree to fight the harmful use of alcohol with global strategy

For the first time, delegations from all 193 Member States of World Health Organization (WHO) reached consensus at the World Health Assembly on a resolution to confront the harmful use of alcohol, which contributes to poor health globally, can devastate families and damage the structure of communities.

Facts on alcohol

Every year, the harmful use of alcohol kills 2.5 million people, including 320,000 young people between 15 and 29 years of age. It is the eighth leading risk factor for deaths globally, and harmful use of alcohol was responsible for almost 4% of all deaths in the world, according to the estimates for 2004.

In addition to the resolution, a global strategy developed by WHO in close collaboration with Member States provides a portfolio of policy options and interventions for implementation at national level with the goal to reduce the harmful use of alcohol worldwide. The resolution endorses the strategy and urges countries to complement and support national responses to public health problems caused by the harmful use of alcohol.

Ten target areas

Ten recommended target areas for policy options include health services' responses, community action, pricing policies and reducing the public health impact of illicit alcohol and informally produced alcohol. WHO was also requested to support countries in implementing the strategy and monitor progress at global, regional and national levels.

"The resolution and the strategy set priority areas for global action, provide guidance to countries and give a strong mandate to WHO to strengthen action at all levels on reducing harmful use of alcohol" says WHO Assistant Director-General Dr Ala Alwan.

Harmful drinking is also a major avoidable risk factor for noncommunicable diseases, in particular cardiovascular diseases, cirrhosis of the liver and various cancers. It is also associated with various infectious diseases like HIV / AIDS and TB, as well as road traffic accidents, violence and suicides.

Implementation

Successful implementation of the strategy will require concerted action by countries, effective global governance and appropriate engagement of all relevant stakeholders. To this end, WHO will also encourage that the strategies to reduce the harmful use of alcohol are included as an integral part of work on global development and in related investment decisions.

For more information contact: Dr Shekhar Saxena, Director, Mental Health and Substance Abuse, Noncommunicable Diseases and Mental Health, WHO/ Geneva. Tel: +41 22 791 3625, Mobile:+41 79 308 9865 E-mail: saxenas@who.int

4. WHO HIGHLIGHTS CRITICAL NEED FOR LIFE-SAVING ANTIVENOMS

With snake bites killing at least 100,000 people a year and countries facing a shortage of appropriate antivenoms, access to and information about available antivenoms is increasingly important. The World Health Organization (WHO) is publishing new guidelines for the production, regulation and control of snake antivenoms and a website with details on where the venomous snakes are located, what they look like, which antivenoms are appropriate, and where they can be obtained.

"Many countries have no access to the antivenoms

they need. Others use antivenoms that have never been tested against their target snake venoms. So often when people get bitten, they can't get the treatment they need," says Carissa Etienne, WHO Assistant Director-General. "These new tools will help bring this to an end."

Global situation

An estimated 5 million people are bitten each year resulting in up to 2.5 million envenomings, at least 100,000 deaths and around three times as many amputations and other permanent disabilities each year. Bites by venomous snakes can cause paralysis that may prevent breathing, bleeding disorders that can lead to fatal haemorrhage, irreversible kidney failure and severe tissue damage that can cause permanent disability and may result in limb amputation.

Victims are mostly women, children and farmers living in poor rural communities, where health systems are not well equipped and medical resources are sparse.

Today, countries face a critical global shortage of appropriate, safe and effective snake antivenoms. A combination of factors has led to the present situation: poor data on the number and type of snake bites, difficulty to estimate the needs and define markets- combined with deficient distribution policies- have contributed to manufacturers stopping production or increasing prices of antivenoms. Poor regulation and marketing of inappropriate antivenoms, has led to a loss of confidence in the available antivenoms by clinicians, public health officials and patients.

The solution

Effective and safe antivenoms requires international collaboration. WHO urges regulators, producers, researchers, clinicians, national and regional health authorities, international organizations and community organizations to work together to improve the availability of reliable epidemiological data on snake bites, the regulatory control of antivenoms and their distribution policies.

The information in the guidelines will assist:

- public health officials in determining what antivenoms are needed in their country and in drafting relevant national public health policies
- national medicines regulators in prioritizing antivenoms for registration and assessing safety, quality and efficacy of antivenoms to meet national public health needs
- procurement agencies in selecting appropriate antivenoms for national treatment needs
- antivenom manufacturers in developing plans for production and sale of appropriate antivenoms
- clinicians and health care professionals in treating snake bites
- general population in knowing and being able to identify which venomous snakes live in their area.

The guidelines provide details for the production, regulation and control of snake antivenoms while the online database identifies venomous snake species for which availability of appropriate antivenoms should be prioritized.

The new guidelines and online database are available at:

www.who.int/bloodproducts/snakeantivenoms

For more information contact: Liz Finney, Communications Officer, WHO. Tel.: +41 22 791 1866; E-mail: finneye@who.int

5. NEW WHO GUIDANCE TO IMPROVE USE OF MEDICINES FOR CHILDREN

The first ever WHO Model Formulary for Children released by the World Health Organization (WHO) provides information on how to use over 240 essential medicines for treating illness and disease in children from zero to 12 years of age. This means that for the first time medical practitioners worldwide have access to standardized information on the recommended use, dosage, adverse effects, and contraindications of these medicines for use in children. A number of individual countries have developed their own formularies over the years, but until now there was no single comprehensive guide to using medicines in children for all countries.

"To be effective, medicines must be carefully chosen and the dose adjusted to suit the age, weight and needs of children," said Dr Hans Hogerzeil, Director of Essential medicines and pharmaceutical policies at WHO . "Without a global guide, many health-care professionals have had to prescribe medicines based on very limited evidence."

The new Formulary is based on the best global evidence available as to which medicines should be used to treat specific conditions, how they should be administered and in what dose. Accurate dosing of medicines for use in children is essential, particularly those between 0-12 months. A dosing error in a child this small can have devastating results.

The Formulary will help health-care providers prescribe the right medicine, in the right formulation and the right dose. It also highlights what precautions to take, what adverse reactions may need to be monitored, and what kind of interactions may occur if

the patient is taking other medications. For example, the Formulary indicates that ibuprofen, which is frequently given to children to treat pain, can have negative interactions when taken with any one of twenty-one listed medicines. It is also important to give this medicine with or after food.

In the case of medicines to treat malaria or HIV, the Formulary highlights the need for better fixed dose combinations - several medicines in one pill - for effective and safe treatment in children. Currently very few fixed dose combinations exist for children; just one anti-malarial and two antiretrovirals to treat children with HIV.

In developing the Formulary a number of areas were identified where more research is needed to provide better treatment for children, such as child appropriate antibiotics to treat pneumonia and specific medicines for neonatal care.

Each year 8.8 million children under five die (2008 data). Many of these deaths are caused by diseases which could be avoided with the use of safe essential medicines formulated appropriately for children. These include diarrhoea and pneumonia as well as conditions such as severe bacterial infections in newborns.

Background information

The release of the first-ever WHO Model List of Essential Medicines for Children identified medicines that should be available for use in children. The development of the WHO Model Formulary for Children builds on the WHO Model List of Essential Medicines for Children, by providing prescribing guidance, and is part of a series of activities WHO has undertaken as part of the "make medicines child size" campaign and the Better Medicines for Children initiative. WHO will support countries to develop their national formularies for children.

For more information contact: Sarah Russell; Communications Officer, WHO; Telephone: +41 22 791 5412, E-mail: russells@who.int

6. MORE THAN FIVE MILLION PEOPLE RECEIVING HIV TREATMENT

World Health Organization advises earlier treatment among people with HIV

An estimated 5.2 million people were receiving life-saving HIV treatment at the end of 2009, according to the latest update from the World Health Organization (WHO).

WHO estimates that 1.2 million people started treatment in 2009, bringing the total number of people receiving treatment to 5.2 million, compared to 4 million at the end of 2008. This is the largest increase in people accessing treatment in a single year.

At the XVIII International AIDS Conference, WHO is calling for earlier treatment for people with HIV. The objective is to begin HIV treatment before they become ill because of weakened immunity.

Estimates developed through epidemiological modeling suggest that HIV-related mortality can be reduced by 20% between 2010 and 2015 if the guidelines for early treatment are broadly implemented.

Earlier treatment can prevent opportunistic infections including tuberculosis (TB), the number one killer of people with HIV. Deaths from TB can be reduced by as much as 90%, if people with both HIV and TB start treatment earlier.

The strength of a person's immune system is measured by CD4 cells. A healthy person has a CD4 count of 1000 - 1500 cells/mm3. WHO previously recommended starting HIV treatment when a person's CD4 count drops below 200 cells/mm3 but now advises starting HIV treatment at 350 cells/mm3 or below.

In addition to saving lives, earlier treatment also has prevention benefits. Because treatment reduces the level of virus in the body, it means HIV-positive people are less likely to pass the virus on to their partners.

WHO's treatment guidelines expand the number of people recommended for HIV treatment from an estimated 10 million to an estimated 15 million. The cost needed for HIV treatment in 2010 will be about US$ 9 billion, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS).

The investments made today can not only save millions of lives but millions of dollars tomorrow. People with weaker immune systems who come late for treatment require more complex and costly drugs and services than those who start treatment earlier and are healthier.

Since 2003 - which marked the launch of the historic "3 by 5" initiative to provide access to HIV treatment to 3 million people living in low- and middle-income countries by the end of 2005 - the number of people receiving HIV treatment has increased 12-fold.

At AIDS 2010, WHO is releasing the 2010 guidelines on "Antiretroviral treatment of HIV infection in adults and adolescents – public health approach", which can be found at www.who.int/hiv.

For more information contact: Tunga Namjilsuren, Team Leader, HIV/AIDS Communications. Tel: +41 79 203