



KMJ

KUWAIT MEDICAL JOURNAL

The Official Journal of The Kuwait Medical Association

EDITORIAL

- What We Need is Not the Will to Believe but the Will to Find Out** 87
Belle M Hegde

REVIEW ARTICLE

- The Knowledge of Teratogenicity in the Prevention of Congenital Anomalies** 89
Adebisi Sunday Samuel

ORIGINAL ARTICLES

- Quantitative Postural Sway Assessment by Computerized Dynamic Posturography in Athletes with Chronic Ankle Sprain and Normal Subjects in Kuwait** 99
Aziz Alfeeli, Ayyoub B Baqer, Mohieldin M Ahmed, Waleed Ahmed Al-Busairi
- Inducible Clindamycin Resistance in *Staphylococcus Aureus*: A Study from a Tertiary Care Hospital of North India** 105
Neha Bansal, Uma Chaudhary, Vivek Gupta
- Allergenicity to Allergens like *Prosopis Juliflor* and Date Tree Pollens in Saudi Arabia** 109
Harb Harfi, Abbas H Alsaeed
- Pregnancy Associated with Brucellosis and Acute Viral Hepatitis: Course and Outcome (Co-infections in Pregnancy)** 113
Serda Gulsun, Vedat Dorman, Selda Aslan, Talip Gul
- Pattern of Chromosomal Abnormalities in Pediatric Acute Lymphoblastic Leukemia (ALL)** 118
Padhi Somanath, Sarangi RajLaxmi, Mohanty Pranati, Das Rupa, Chakravarty Sukumar, Mohanty Raghmani
- The Diagnostic Value of Sinus-Track Cultures in Secondary Pediatric Chronic Osteomyelitis** 125
Mehmet Ulug, Celal Ayaz, Mustafa Kemal Celen, Serdar Necmioglu

CASE REPORTS

- Multifocal Solitary Subungual Glomus Tumors in a Patient with Neurofibromatosis Type 1** 130
Sabyasachi Ghosh, Mohammad Abdur Rashid, Ravidran Gopal
- Laparoscopic Appendectomy in the Third Trimester of Pregnancy: Report of Two Cases and Description of Technique** 133
Waleed Al-Bastaki, Waleed Buhaimed, Khalid Al-Zamel
- Autoimmune Adrenal Insufficiency Antedates the Diagnosis of SLE, Does It Really Matter?** 136
Ebtihal Aljamaan
- Macroinvasive Papillary Thyroid Carcinoma Presenting as Internal Jugular Vein Tumor Thrombus** 139
Ayman Farouk Elezeby, Ibrahim Alenezi, Medhat Mohamed Saber Elsherbiny
- Late-Onset Chylothorax after a Pneumonectomy for Lung Cancer: a Case Report** 143
Ata Ozturk, Ali Alper Gulle, Soner Gursoy
- Thyroid Hemiogenesis: Case Report and Review of Literature** 146
Rasheed Fadel Said Alsaleh, Abdulrahman Faraj Mawi Almutairi, Yousef Ahmed Saleh Hussein
- Buried Bumper Syndrome** 150
Abdullah Al-Muhaiteeb, Sahasranamaiyer Narayanan

KUWAIT MEDICAL JOURNAL

C O N T E N T S

Continued from cover

LETTER TO THE EDITOR

Blount Disease: Bowlegs may not Always be Physiological

Ayşe Esra Yılmaz, Hakan Atalar, Tugba Tas, Nurullah Celik

153

SELECTED ABSTRACTS OF ARTICLES PUBLISHED ELSEWHERE BY AUTHORS IN KUWAIT

154

FORTHCOMING CONFERENCES AND MEETINGS

159

WHO-FACTS SHEET

166

1. Obesity and Overweight
2. Antimicrobial Resistance
3. Visual Impairment and Blindness
4. Some 2.6 Million Babies Stillborn in 2009
5. Urgent Action Essential to Protect Malaria Therapies

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Article

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

Book

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

Book chapter

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

Weblinks

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

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Editorial

What We Need is Not the Will to Believe but the Will to Find Out

Belle M Hegde

The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*
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Kuwait Medical Journal 2011; 43 (2): 87-88

"The illogical man is what advertising is after. This is why advertising is so anti-rational; this is why it aims at uprooting not only the rationality of man but his common sense."

Henryk Skolimowski

There are demands growing all over the world for rationality in medical interventions these days, not the least in the UK and the USA. In fact, the first editorial in British Medical Journal for the year 2011, to be published during the first week of January, is on rationality in medical interventions. I congratulated the editor for her bold stand on opening the Pandora's Box on rationality in medical interventions - drugs or surgery. Going through the history of the word rational, I found that way back in 1803 the meaning was: "to explain, to make reasonable;" in the psychological sense of "to give an explanation that conceals true motives." It dates from 1922.

There is a nice movie, Big Bucks, Big Pharma, on this topic which is worth watching. I shall give the readers a glimpse into that movie here. "Big Bucks, Big Pharma, pulls back the curtain on the multi-billion dollar pharmaceutical industry to expose the insidious ways that illness is used, manipulated, and in some instances created, for capital gain. Focusing on the industry's marketing practices, media scholars and health professionals help viewers understand the ways in which direct-to-consumer (DTC) pharmaceutical advertising glamorizes and normalizes the use of prescription medication, and works in tandem with promotion to doctors. Combined, these industry practices shape how both patients and doctors understand and relate to disease and treatment.

Ultimately, Big Bucks, Big Pharma challenges us to ask important questions about the consequences of relying on a for-profit industry for our *health and well-being.*" (Italics mine!)

There is an apt comment on this movie by an American movie critic: "In my opinion this is the best made film on our site today regarding the pervasiveness of drug companies in our every day lives. The film starts with narration by the famed journalist Amy Goodman but lets the interviews themselves narrate the film later on. Though this film doesn't address the subject directly, if you want to know why the United States does not provide universal healthcare, I think that you should watch this movie. Why should we have free or inexpensive healthcare, if the current system is so profitable?!"

I think our present therapeutics and its attendant pseudo-science would be correctly described by this meaning of the word - rational. The industry that tries the marketing strategy of rationalizing drug pushing and disease mongering by concealing their true motive - to make the highest profit for themselves - can never be altruistic to listen to your sane advice. Your story of Insulin pens was one such effort. Now many other drugs have come with pens! I am reminded of what Bernard Mandeville, the guru of Laissez Faire said, when he wrote: "In the corporate economy profit is the sole motive irrespective of consequences." How very true? Mandeville was Adam Smith's teacher! Our drug cartels have taken his advice to their heart.

Taking your advice in the New Year, I hope some one will come up with audits like the one which showed aspirin in its true colour for all the newly introduced drugs. Remember we have had digoxin for nearly

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

350 years from William Withering's time. Even now the DIG (digoxin investigation group) group recently failed to find out why digoxin is prescribed for heart failure patients in sinus rhythm? Why is the ADR death rate going up exponentially with "so called" scientific advances in modern medicine? Was not Hillary Butler right in saying that the present day modern medicine, which has become a corporate monstrosity, would have cut many James Wakelys in the knees. James Wakely was a young doctor in London and a member of the House of Commons who thought in early nineteenth century that the medical profession at that time had become a bad abscess on the body of society which he wanted to cure by taking out the pus using a surgical lancet. He started the now famous medical journal, The Lancet, for that purpose in 1823 AD. He had assessed the profession at that time to be a bunch of "incompetent, corrupt and nepotistic bunch of crooks." Poor man, even after nearly two hundred years, the abscess that modern medicine then was, is only growing bigger by the day despite his The Lancet!

Even the President of NICE, Sir Michael Rawlins, in his Harveian oration at the Royal College, had this to say about RCTs: "that randomized controlled trials (RCTs), long regarded as the 'gold standard' of evidence, have been put on an undeserved pedestal". Sir Michael outlines their limitations in several key areas, arguing that a diversity of approaches should be used to analyze the whole of the evidence base. (Rawlins M, The Harveian Oration of 2008, De Testimonio, On the evidence for decisions about the use of therapeutic interventions, Royal College of Physicians, 2008).

Let me remind the readers that the "first pass effect" that we, medical students all over, memorized

for the pharmacology examination must have given us the warning that all (I mean all) reductionist chemical molecules, ranging from aspirin to rosiglitazone, are alien to the human system. The body tries to get rid of them. This has now been demonstrated by Douglas C Wallace using his soft ware MITCHIP to be true! (Genetics 2008; 179: 727) You will have the same story for your editorial every year end to welcome the next New Year, if we do not learn from our mistakes. We need another Bernard Shaw to write a drama on Patients' Dilemma today.

When you watch the movie cited above you will come to know how people like you are brainwashed to ask for those wonder drugs, advertised daily as panacea for this or that disease, from your doctor. Many times it is likely that you might even imagine a disease (disease mongering by the industry) to have the treatment "very early". How does the common man, even the literate one, survive in this polluted atmosphere where the industry and the profession seem to be in cahoots with one another for personal gain? To add to this a new industry has grown around this rationality - corporate hospital industry, especially in the developing countries like India, where even today more than 400 million people get less than one clean nutritious meal a day. Sixty-seven million children suffer from nutritional immune deficiency syndrome (NIDS) dying by the thousands daily! Let us have a heart.

"Appeals to rationality are mostly bluff. There is no good theory of what it is nor of how to recognize it."

Mellor, D H

Review Article

The Knowledge of Teratogenicity in the Prevention of Congenital Anomalies

Adebisi Sunday Samuel

Department of Human Anatomy, Faculty of Medicine, Ahmadu Bello University, Zaria, Nigeria

Kuwait Medical Journal 2011; 43 (2): 89-98

ABSTRACT

A considerable number of pregnant women need to take ongoing medication for existing health problems such as acute respiratory infection or pregnancy complications like eclampsia. It can be dangerous for such women to avoid prescription drugs, should they have a medical condition or become ill; without treatment, the health and welfare of both the mother and her unborn baby could be at increased risk. Unfortunately, research has shown that women who consumed potentially teratogenic drugs – prescribed or not - during pregnancy had very little information about these drugs and even less information about their effect during pregnancy. For this reason, adequate knowledge of this phenomenon is required both by the pregnant women, to heed necessary precautions and health workers, to give the

needed advice - prior to and during gestation - with the onerous task to prevent or reduce the incidence of birth of monsters. Wide consultation was made in the archives and contemporary literature to obtain and compile detailed information on the subject and make them available to interested readers, in particular the pregnant women, health workers and researchers in this field. This paper presents some of the earlier and recent works and publications on the subject, to update knowledge and information. Although presently knowledge is inadequate to combat the incessant menace of birth with defects, the available information, if well publicized and utilized, will help to guarantee the good health of the mother and normal development of the conceptus and hence, lessen the incidence of malformed babies.

KEY WORDS: conceptus, health workers, malformation, pregnancy, teratogens

INTRODUCTION

Teratology from the Greek word *teras*, meaning “marvel” or “monster” is the science dealing with the causes, mechanisms, and manifestations of developmental deviations of either structural or functional nature otherwise known as congenital anomalies or malformations. These structural or functional abnormalities are present at birth although they may not be diagnosed until later in life. They may be visible on the surface of the body or internal to the viscera. Congenital malformations account for approximately 20% of deaths in the perinatal period^[1-3]. Hence, this necessitates interest in the knowledge about the effect of maternal environmental factors on the conceptus during development, as one or combination of these factors may act to derail the normal course, leading to aberrations. Such factors responsible for this deviation are known as teratogens. A teratogen therefore, is a drug, chemical, virus, infectious agent, physical condition, excess or deficiency that, on fetal exposure, can alter fetal morphology or subsequent function in postnatal life. However, teratogenicity

depends upon the ability of the agent to cross the placenta; for instance, certain medications such as heparin cannot^[4-6].

In general, drugs, food additives, and pesticides are tested to determine their teratogenicity to minimize exposure of pregnant women to teratogenic agents. To prove that a specific agent is teratogenic means to prove that the frequency of congenital malformations in women exposed to the agent is prospectively greater than the background frequency in the general population. These data are often times not available for humans and thus cannot be determined in an unbiased fashion. Therefore, testing is often done in animal models and often times the drug is administered at higher than the usual therapeutic doses. However, there are clearly species differences between teratogenic effects, limiting this testing in animals^[7-9].

However, some exposures when tested could be categorized as potent (proven) teratogens (Table 1)^[10-26]; or probable (possible) teratogens (Table 2)^[27-29], based on the following criteria:

- A recognizable pattern of anomalies

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Table 1: Some proven human teratogens^[10-26]

Alcohol	Fetal alcohol syndrome Affects skeletal and nervous tissues
Carbamazepine	Neural tube defects
Cocaine	Abruptio placentae, fetal mortality, low birth weight, microcephaly, limb and urinary tracts malformations
Coumarin	Nasal hypoplasia, eye defects, hearing loss, Calcific stippling of the epiphyses
Diethylstilbestrol	Cell adenocarcinoma of vagina in patients who receive its treatment during first trimester
Aminopterin	Fetal mortality
Phenytoin	Fetal hydantoin syndrome
Isotretinoin	Retinoic acid embryopathy
Lithium	Ebstein's anomaly
Misoprostol	Limb anomalies
Tetracycline	Yellow-brown discoloration of teeth
Thalidomide	Malformations of tissues of mesodermal origin-Limbs, cardiovascular, ear and gut musculature
Retinoic acid	Craniofacial dysmorphisms, cleft palate, thymic aplasia, and neural tube defects
Tetracycline	Yellow staining of the primary or deciduous teeth and diminished growth of the long bones
Nicotine	Intrauterine growth restriction, premature delivery, adverse effect on mental development
Androgenic agents	Masculinisation of female fetus, ambiguous external genitalia
Busulfan	Stunted growth, skeletal anomalies, corneal opacity, cleft palate
Methotrexate	Facial skeletal and vertebral malformations
Trimethadione	V-shaped eyebrow, low set ear, cleft lip and palate
Lead	Misscalcificatio, retarded fetal growth
<i>Cytomegalovirus</i>	Microcephaly, microphthalmia
<i>Rubella virus</i>	Cataracts, glaucoma, congenital heart defects
<i>Varicella</i>	Skin scarring, muscle atrophy, mental retardation
<i>Treponema pallidum</i>	Hydrocephalous, congenital deafness
<i>Toxoplasma gondii</i>	Microcephaly, cerebral calcification
<i>Herpes simplex virus</i>	Retinal dysplasia, microcephaly, microphthalmia
<i>Asparagus racemosus</i>	Fetal growth retardation, resorption
Enrofloxacin	Feotal resorption, growth retardation
Uranium aerosol	Hydrocephalous, congenital deafness
Bromocritine	Hydrocephaly, heart defects, abnormally small head, limb reduction defects, failed development of kidneys

- A statistically higher prevalence of a particular anomaly in patients exposed to an agent than in appropriate controls
- Presence of the agent during the stage of organogenesis of the affected organ system
- Decreased incidence of the anomaly in the population prior to the introduction of the agent
- Production of the anomaly in experimental animals by administering the agent in the critical period of organogenesis
- Agents are classified as non-teratogenic if they fall under category A or B according to use-pregnancy rating (US FDA, '79)^[10-12]

Teratogens can be prescription / non-prescription medications, illegal drugs, vaccines, illnesses, environmental exposures, occupational exposures, or maternal autoimmune disorders^[30]. The resulting congenital malformations, namely, the non-reversible functional, metabolic or morphological defects may be detectable at birth or only later in life. According to Wilson^[31], the following six principles normally apply to teratogenesis:

- Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with adverse environmental factors
- Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to an adverse influence. There are critical periods of susceptibility to agents and organ systems affected by these agents.
- Teratogenic agents act in specific ways on developing cells and tissues to initiate sequences of abnormal developmental events
- The access of adverse influences to developing tissues depends on the nature of the influence.

Table 2: Some possible human teratogens^[27-29]

Name	Effects
D-penicillamine	Connective tissues disorder (cutis laxia)
Methimazole	Scalp defects (aplasia cutis congenital)
Diazepam	Cleft lip and palate
Artesunate	Skeletal and nervous tissues
6-mercaptopurine	Inflammatory bowel disease

Several factors affect the ability of a teratogen to contact a developing conceptus, such as the nature of the agent itself, route and degree of maternal exposure, rate of placental transfer and systemic absorption, and composition of the maternal and embryonic/fetal genotypes.

- There are four manifestations of deviant development (death, malformation, growth retardation and functional defect).
- Manifestations of deviant development increase in frequency and degree as dosage increases from the no observable adverse effect level (NOAEL) to a dose producing 100% lethality (LD100)^[31].

MECHANISMS OF TERATOGENICITY

Medical science cannot always predict how exposure to a teratogenic drug will affect a fetus. The potential to harm depends on a range of factors as stated by Wilson^[31]. Other factors, such as maternal diet, maternal age, Rh factor, and physical condition such as stress or distress, illness – all these could singly or jointly play a role. Some teratogens are associated with recognizable patterns of malformations: for example, thalidomide produces limb phocomelia, while valproic acid and carbamazepine produce neural tube defects, alcohol with fetal alcohol syndrome, phenytoin with fetal hydantoin syndrome and coumarin anticoagulants with fetal warfarin syndrome^[32-35].

In any case, some of the pathways by which teratogens could possibly potentiate their toxic effects have been well examined and succinctly highlighted as being through any of the following: folate antagonism – such as aminopterin; enzyme-mediated teratogenesis; oxidative stress – such as nutritional deficiencies, hypoxia or environmental chemicals; functional disruptions in the neural crest cells; disruption in the vascular system or disturbed endocrine systems – such as cortisone, progestin. Teratogens could also trigger off the disruption of carbohydrate metabolism in maternal diabetes^[34-36].

On the other hand, teratogenic agents may bind to transcription factors and prevent the proper production of functional proteins. For example, PCBs bind to a ligand-activated transcription factor called the Ah receptor, leading to the increased induction of the cytochrome P450 enzyme, which forms reactive intermediates that bind to DNA. The toxic agent, dexamethasone, can bind to the glucocorticoid receptor (instead of its endogenous ligand or cortisol), forming a complex that tightly binds to DNA. This promotes the transcription of genes that increase gluconeogenesis at the expense of essential lipid and protein synthesis, thus leading to apoptosis of lymphocytes and teratogenesis. Mercury is another example of a toxic agent that can bind to DNA and lead to the translation of dysfunctional proteins in the brain and kidneys.

Toxic agents can harm DNA through strand breakage, oxidation, alkylation, large bulky adducts (between mismatched base pairs), or the induction of mutations. Incorrect expression can also occur when toxic agents bind to elements critical to the transcription and translation of genes, such as transcription factors^[37,38]. Moreover, teratogenic agents can induce cell death by apoptosis and necrosis^[39].

TRANSFER OF TERATOGENS ACROSS THE PLACENTA

On the ability and rate of transfer of teratogens across the placenta, earlier reviews include those of Mirkin and Singh^[40] and Waddell and Marlowe^[41]. These authors reported the differences in transfer as a combined function of route of administration of the materials and the animal models in use, since rapidity and extent of crossing the placenta into the fetus by drugs and chemicals are by no means measures of the toxic action on the fetus or the persistence of the compound in the fetal tissues^[42]. The rate of transfer of a chemical across the placenta depends on the net sum of many factors: molecular size, lipid solubility, protein binding, pH gradients *etc.* Small molecules, less than 600 molecular weight and low ionic charge cross by simple diffusion, active transport, pinocytosis or perhaps also by leakage. Lipophilic chemicals are known to cross the placenta and other membranes more readily than other compounds^[43]. It now seems that the rate as determined by size, charge, lipid solubility, affinity to complex with other chemicals and so on, all play a significant role in placenta permeability. For instance, ethanol with a molecular weight of 46.07 has been shown to pass across the placental barrier and that its concentration in the fetus is almost as high as in the mother^[44].

SITE OF ACTION OF TERATOGENS

Unfortunately, knowledge of the certainty of the specific site of action of the teratogenic agents within the maternal-placenta-fetal unit is yet obscure. All too frequently, the naive assumption is made that the administered agents find their way to the fetus and directly interfere with the growth and differentiation of these cells. Not only is such evidence not available, but a large number of clues actually indicated that these chemicals do not act directly on fetal cell. For instance, it had been pointed out that the concentration of the teratogen, cortisone was not higher at its site of teratogenicity in the fetus than it was in any other fetal tissues and its site of action, and that its concentration in all the tissues was lower than in the maternal tissues^[41]. Comparison of maternal fetal concentration ratios of variety of chemicals with low or high teratogenic potential revealed that the tendency was considered to be that, the potent teratogens have high fetal maternal

ratios^[41]. Hence, clearly the earlier naive assumption is untenable that 'the greater the amount of chemical reaching the fetus, the more likely the production of fetal anomalies. In light of this puzzle, the problem has now become a search for the sites within the entire maternal-placenta unit. Lately, the predominant direction of reports are on the action that produces anomalies by their effects on the placenta, and that the direct effects of the agents on the mother may be as frequent as those acting directly on the fetus. However, the total dose of a chemical reaching the conceptus is a product of interaction of many variables, some relating to the maternal functional capacity, others undoubtedly reflecting the complex characteristics of the placenta. The possible interruption of utero-placental blood flow by the chemical has also been suggested^[45,46].

NUTRITIONAL ROLE IN TERATOGENESIS

The role of maternal nutrition in the potentiation of the toxicity or teratogenicity of an agent cannot be undermined. For a long period of time, the association of malnutrition of the mother with malformations of the fetus was subjected to debate. This brings us to consider and justify the proponent of the fetal origin hypothesis, which opined that the postnatal health may be influenced by prenatal factors^[32,47,48]. This hypothesis argues that the environment experienced during the individual's prenatal life 'programs' the functional capacity of the individual's organs, and this has a subsequent effect on the individual's health. For instance, when the fetus experiences a poor nutritional environment, it develops its body functions to cope with this, with the idea that the environment experienced prenatally is the one that it expects to continue experiencing, and thus, its body develops to cope with it - a predictive adaptive response mechanism^[47,48].

Exposure to a drug or chemicals for a brief period of time depriving the normal nutrient for only that period might be expected to have relatively little impact. Severe reduction in protein and caloric intake during the first 10 days of pregnancy in the rat followed by a return to an adequate diet prolonged the gestation, but the weight of the newborn was normal; the only deficit noted from early deprivation of protein during gestation was a deficit in cerebral protein content at birth. It had also been noted that administration of morphine to pregnant rabbits was associated with reduction in fetal and placental weight^[49]. Moreover, some workers have argued against nutritional deficiency as a possible mediator or potentiator of teratogenicity. According to these investigators, there was no evidence that the nutrition of women giving birth to infants with fetal alcohol effect (FAE) or fetal alcohol syndrome (FAS) is any worse than those women whose infants do not have these problems even though their mothers drank equally heavily^[50]. However, it appears that enough evidence is available to establish the fact that

maternal nutritional deficiency is a possible teratogenic potentiator and this has been amply demonstrated in the rats^[51] and in humans^[48]. For instance, vitamin A deficient diet fed to pregnant rats on the 10th day of gestation caused mainly cardiac abnormalities whereas when administered up to the 15th day, resulted in ocular, aortic, lung and diaphragmatic defects^[52,53].

GENETIC ROLE IN TERATOGENESIS

The genetic make up of the developing organism is the setting in which induced teratogenesis occurs. Differences in the reaction to the same potentially harmful agents by individuals, strains and species are presumed to depend on variations in their biochemical or morphological make-up, which are in turn determined by genes^[54,55]. The fact that the mouse embryos are usually susceptible to cleft palate induction by glucocorticoids whereas most other mammalian embryos are resistant to these agents can be interpreted to mean that mice possess inborn chemical or anatomical features which make them more vulnerable (less resistant) to these agents than are other animals and these are at least to some extent genetically determined. Thus, the same sort of determinants that gives rise to individuals, strains and species their distinctive similarities and dissimilarities in normal structure and function probably give them varying degree of susceptibility to adverse influences^[54]. To this end, it has been suggested that the occurrence of anomalies is in part a measure of the inability of genetic and other regulatory mechanisms to overcome the adverse localized sensitivity of the embryo to an external intrusion. This could be explained from the fact that chromosomal aberrations induced in somatic cells are the cause of malformation following exposure to teratogens. In the light of this knowledge, differences between model systems and man emphasize some of the reasons for the perceived low level of predictability of animal tests for man. Therefore, the level of confidence in the ability of these animal studies to be predictive for man remains far from high. Only when the mechanism of teratogenesis and the factors affecting species differences in teratogenic response are understood will we have confidence in the predictive accuracy of animal studies. Although major new teratogenic drugs in humans have been predicted from animal studies, there are problems in extrapolating animal data to humans, and this has since, been a matter controversy^[56-59]. For instance, animals have a different "gestational clock" to humans, there is marked interspecies variability in susceptibility to teratogens and no experimental animal is metabolically and physiologically identical to humans^[54]. In any case, animal studies are important because, in some instances, they have shed light on mechanisms of teratogenicity and moreover, when an agent causes similar patterns of anomalies in several species, human teratogenesis should also be suspected.

Above all, for obvious ethical considerations no studies of teratogenicity are conducted during embryogenesis in humans^[43]. On the other hand, reports have shown that in some cases, genetic vulnerability is related to the sex of the developing organism. Male embryos and fetuses are at a greater risk than female in that more male embryos are more often aborted spontaneously; newborn boys have more birth defects, and older boys have more learning disabilities and other problems caused by behavioral teratogens^[47, 60-63].

In any case, whether it is the maternal or fetal component of genetics that is more important in determining the extent of the effect of teratogens is not yet well understood. It appears, for instance, that the rate of maternal alcohol metabolism could modify the effects of alcohol on the fetus^[40] although it has been reported that not all the offsprings of alcoholic women manifest the characteristic features of FAS and hence, the rate of maternal alcohol metabolism could not have modified the effects of alcohol metabolism on the fetus.

In the same light, studies conducted on fourteen pairs of identical twins born to heavily alcoholic women showed these children exhibiting FAS of differing severity and in addition, significant differences in the individual rate of ethanol metabolism ranging from a low value of 0.11 mg / ml/ h to a high value of 0.24 mg / ml/ h. This is indicative of a possible dominance of the fetal genetic make-up over that of the mother in determining the severity of the toxic or teratogenic effect of ethanol on conceptus in utero^[40].

EFFECTIVE DOSAGE OF TERATOGENS

Considering the dosage of an agent, not all dosage levels of known teratogens are potent enough to trigger-off any response. There are lower (sub threshold) dosages, which apparently do not affect the normal development of an embryo and even the mother, and lethal dosages, which will cause death of both the fetus and even the mother. Between these two extremes is a narrow 'teratogenic zone' in which the dosage is sufficient to interfere with specific development without destroying the whole embryo. In addition, the frequency of administration of teratogens determines more or less the extent of its action. For instance, it was observed in a study on mice exposed to 100r of X-rays on the 9th day of gestation, many types of malformations in almost all the fetal tissues were recorded. The same treatment on day 10 caused deformities in 75% of the offsprings, whereas further treatment on the 11th day produced no deformities of any tissue^[64].

It could therefore be concluded that an appropriate dosage of a known teratogen administered at the appropriate time of development in a given species will cause developmental disturbances. Cell death observed in teratogen-treated embryonic organs destined to be

malformed must occur selectively and within a critical period of time for a birth defect to result^[31,32]. Low doses of cytotoxic agents may produce levels of cell death that can be replaced through restorative hyperplasia of surviving cells, resulting in the formation of small but morphologically normal fetuses. High doses that cause damage to too many cells and organ systems to be compatible with life result in embryo lethality. Cells dying from teratogenic treatment must be replaced by proliferation of surviving cells within a critical period of time to avoid dysmorphogenesis. For instance, during the period from conception to implantation (2 weeks), there is a relative resistance to drug effects. Exposure during this time produces an "all or none" effect, that is, either zygote dies or it is unaffected since the embryonic totipotent cells could replace the damaged cells. A cytotoxic drug such as hydroxyurea (HU) kills mesodermal cells in the limb buds. Surviving cells attempt to replace the cellular deficiency by restorative proliferation. If the replenishment occurs by the critical time when digits are formed by mesenchymal condensation, then limbs with normal amounts of digit are formed; if not, ectodactyly and missing ribs occur^[43].

EFFECTS OF TERATOGENS ON DNA SYNTHESIS

Some cytotoxic agents at lower dosage suppress DNA synthesis and cell division without causing cell death. Depressed proliferative activity in itself may contribute to teratogenesis by reducing the number of cells available for the formation of tissues during the organogenesis. Many agents that depress DNA synthesis are known to be teratogenic. Yet it is not clear that depression of DNA synthesis alone can lead to birth defects. The cell deaths that accompany inhibition of DNA synthesis are believed to be more important correlates to dysmorphogenesis. The relationship between depression in DNA synthesis and teratogenesis has been examined in a study of cysteine arabinoside (Ara - C) induced birth defects. Further study suggested that the teratogen action was not inhibition of DNA synthesis alone but rather the cytotoxicity that accompanied it. In a similar study with hydroxyurea (HU), Ara-C and aminothiadiazole (ATD), the same relationship between the depression of DNA synthesis and cell death was observed^[60]. It is generally believed that tissues with high proliferative activity are more likely to exhibit cell death after teratogen treatment than those with low proliferative activity. Although this may form a partial basis for the response of specific target organ to such an agent, there are cases that cannot be explained solely on these terms, for example, the effects of cyclophosphamide on RNA polymerisation in various parts of the rat embryos on day 13 of gestation. They found that those cells which were still proliferating but had begun differentiation

were most severely affected by cyclophosphamide as in the case of the forelimb on day 13 of gestation. In contrast, the hind limb that rapidly proliferates was less severely affected. These authors suggested that cyclophosphamide exerts teratogenic effect on its target by disturbing the RNA metabolism, which varies according to the state of differentiation of the cell^[61-63].

Pharmaco-kinetics and metabolic factors in general do not appear to play an important role in target organ specificity of teratogens. During the organogenesis period in rodents the embryo has little capacity to activate drugs *via* mixed function oxidase metabolism. The amount of cytotoxic agents reaching the cell, differential drug distribution, permeability of cells to the agent and amount of intra-cellular binding do not appear to be important factors in determining which embryonic organ systems are damaged, but rather intrinsic cell differences related to rate of proliferation and differentiative state appear to determine which cells are susceptible to teratogenesis^[61].

So far as the depression in DNA synthesis and cell death is concerned in embryonic as well as adult tissues treated with teratogenic agents, cytotoxicity can be assumed to be a common biological property of these agents. Whether or not birth defects results from the cytotoxic response of the embryos, teratogenesis depends upon gestational time of treatment (proliferative and differentiative state of the target organ), and the extent of cell death^[62].

MUTATION IN TERATOGENESIS

Mutagen is an agent - toxin, radiation, virus - capable of causing mutation, that is, a relatively permanent change in DNA, the hereditary material. The amount of damage caused by a mutagen depends on three factors: (1) chemical reactivity between DNA and the mutagen, (2) the concentration or dose of the mutagen, and (3) length of exposure time of DNA to mutagen. Damage and repair to DNA are constantly occurring; but when the damage is not repaired the result can be cancer or cell death. Also, genetic diseases such as cystic fibrosis and sickle cell disease can be caused by a single DNA mutation in one gene^[65].

Mutation is a permanent alteration in DNA produced by base-pair substitutions, frame-shift mutations, aneuploidy / polyploidy (gain or loss of chromosomes), or chromosome aberrations (deletion, translocation, duplication). If mutations occur in germ cells, they can lead to teratogenic effects. For example, acrylamide found in some pre-cooked and processed foods can cause reduced fertility in males^[38]. The role played by mutation as a fundamental mechanism in teratogenesis has been receiving little experimental attention, even though somatic mutation is postulated to be one of the underlying causes of birth defects. Mutagenic lesions are believed to be distinguishable

from teratogenic responses in that the former are transmissible to future generations, whereas the latter are confined to a single generation. The lack of experimental examination of mutagenesis could be due to the prominence of teratogenic damage. Dead cells cannot transmit genetic defects to progeny cells. The belief that teratogenesis occurs when more cells are removed from a population of cells destined to form an organ rudiment that can be replaced by restorative hyperplasia within the critical period needs to be re-examined. Cell death invariably accompanies chemical induced heritable mutation and transformations, but it is not believed to be causative factor in these genetic alterations. It seems logical that DNA damaging lesions could be the initial event to cell death^[66-70].

REPARATIVE GROWTH FOLLOWING TERATOGENESIS

The importance of reparative processes in the final expression of malformation after teratogenic insults has not been given adequate consideration in the field of teratology. For most teratogenic agents, a threshold dose exists below which abnormal development cannot be detected^[43]. This 'threshold' changes throughout gestation and there are developmental stages, that is, during organogenesis period, during which embryo is highly resistant to teratogenic insults. Implicit in this concept of a threshold dose is that the embryo possesses a varying capacity at different developmental stages to repair teratogenic damage^[43]. Repairs of teratogenic insults during the organogenesis period which hitherto had traditionally been viewed in terms of tissue regeneration or of restorative hyperplasia of the surviving cells to replace dead cells undergoing necrosis from teratogenic insults would be interesting to investigate. Study of the differential capacity of cells surviving teratogenic insults versus those that die may contribute to an understanding to the process of cell death. Correlation of the time dependent insults with the rate of repair of DNA damage may help elucidate the target organ specificity of certain teratogens. For example, the question may be asked: are embryonic limbs susceptible to teratogenic insults on day 11 of gestation but not on day 14 due to a depressed capacity of the day 11 bud to repair DNA damage? Such questions yet need to be addressed as earlier workers in this field had pointed out^[43].

The processes whereby embryos cope with teratogenic assaults are fundamental to understanding the mechanisms of teratology. A deleterious response may occur only after the defense mechanisms are overwhelmed. Embryonic repairs had traditionally been regarded in term of tissues regeneration. The critical lesions, however, involve injury to individual cells. Detailed analyses of the capacity of the embryonic cells to repair lesions in DNA during the organogenesis

period contribute to an understanding of the basic mechanism of teratogenesis^[43].

NON-TERATOGENIC MEDICATION

It could, however, be noted that some exposures are non-teratogenic and safe to use in pregnancy. Such include spermicides - agents which impair the ability of sperm to fertilize an egg; acetaminophen - the active ingredient in some pain relievers; prenatal vitamins - such as folic acid and folic acid, which are prescribed when a woman becomes pregnant to supplement her diet to meet the growing nutritional needs of pregnancy. When used at the recommended dosage, prenatal vitamins do not increase the risk for birth defects. Also, non-ionizing radiation - such as ultraviolet rays (sunlight) and microwaves are not teratogenic as microwaving food while pregnant is not known to increase the risk for birth defects or health problems^[71].

PREVENTION OF CONGENITAL ANOMALIES

Although, the use of teratogenic drugs may have to be continued in severe maternal diseases such as epilepsy and cancer^[72-76], the use of non-teratogenic drugs in less severe (non-life-threatening) diseases may lessen or even prevent the occurrence of teratogenicity in conceptus in addition to possibly alleviating the consequent effects in maternal disease^[77-79]. For instance, periconceptional folic acid-containing multivitamin supplementation can prevent the major proportion of neural-tube defects^[80-85]. In any case, there are many preventive measures that could be taken on a population and individual level that could now, or after more research, avoid or reduce the risk of congenital anomalies from arising in the first place. These interventions include the following among others:

1. Nutrition - for instance, folic acid supplementation or fortification: Folic acid (through diet and supplementation) has been shown to decrease the risk of neural tube defects (NTDs) by 50 - 70% and also decrease or minimize other specific birth defects including congenital heart disease, urinary tract anomalies, oral facial clefts, limb defects, and pyloric stenosis. In women with no history of previous NTD, a preventive dose of folate (preconception through the first trimester) is 0.4 mg / d. In women with a history of a previous NTD, the dose is 4.0 mg / d.
2. Prevention of maternal infection and disease, *e.g.*, rubella vaccination and periconception care for women with epilepsy or diabetes
3. Preconception glycemic control
4. Avoidance of teratogenic drugs
5. Controlling of chemical exposures from occupational and environmental sources

6. Special action on pregnancy exposure for major health determinants such as smoking, alcohol, and obesity
7. Identify, prevent and treat cases of substance abuse

In addition, the following steps should also be taken to prevent birth defects related to maternal environment:

- Administer appropriate vaccinations before conception, *e.g.*, varicella, measles, mumps and rubella
- Identify and treat maternal disease such as diabetes before and during pregnancy
- Known or suspected teratogens should be avoided
- Most drugs should, as much as possible, be avoided during the most vulnerable period of organogenesis, that is, the first trimester.
- Diagnosis of congenital anomalies and termination of pregnancy are controversial issues on cultural and religious grounds and hence, care should be taken before this measure could be resorted to^[86-93].

CONCLUSION

Recognition of human teratogens offers the opportunity to prevent exposure at critical periods of fetal development and affords possible prevention of certain types of congenital malformations. The use of teratogenic drugs should be avoided during pregnancy. Moreover, recent effective ultrasound scanning can detect major fetal defects by about the 18th - 20th week of gestation with a high degree of efficacy. If serious fetal defects are detected, the couple can then be given information to help them decide whether to terminate the pregnancy or not.

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Original Article

Quantitative Postural Sway Assessment by Computerized Dynamic Posturography in Athletes with Chronic Ankle Sprain and Normal Subjects in Kuwait

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ABSTRACT

Objective: To identify quantitative postural sway assessed by unilateral stance test using computerized dynamic posturography in athletes with chronic ankle sprain and normal subjects in Kuwait

Design: Retrospective case control study

Setting: Sports and balance clinics, Physical Medicine and Rehabilitation Hospital, Ministry of Health, Kuwait

Subjects: Twenty six male athletes suffering from chronic ankle sprain and twenty two healthy individuals as a control group well-matched for age and sex were included in this study.

Intervention: Clinical assesment and computerized dynamic posturography

Main Outcome Measures: Mean centre of gravity (COG) sway velocity which displays COG stability with eyes open

and eyes closed was computerized and assessed.

Results: A significant increase of mean (\pm SD) COG sway velocity on left or right leg standing with eyes open and eyes closed of athletes with chronic ankle sprain as compared to control group was found ($p < 0.05$). In addition, the mean (\pm SD) percentage difference score with eyes open and eyes closed in athletes with chronic ankle sprain was higher compared to control group ($p < 0.001$).

Conclusion: Patients with chronic ankle sprain have a higher COG sway velocity and impaired postural sway compared to normal subjects. The unilateral stance test may be used to identify quantitative postural sway and balance in chronic ankle sprain. The ligamentous damage, ankle muscle strength deficits and proprioception deficits at the ankle joint may explain poor balance in ankle sprain.

KEY WORDS: ankle sprain, computerized dynamic posturography, unilateral stance test

INTRODUCTION

Ankle sprains are the most common injuries in running and jumping sports, such as basketball, soccer, and volleyball^[1]. Chronic ankle instability, sometimes associated with multiple ankle sprains, can lead to difficulty with walking, running and jumping^[2]. Recurrent ankle sprains may lead to chronic instability especially among active individuals. According to Holme *et al*^[3] lateral ankle sprains are common and account for nearly 15% of all sports injuries. Ankle sprains vary in severity and consequential disability based on the degree to which the ligaments are damaged. In most cases, ankle sprains are graded as mild, moderate, or severe^[4]. The incidence of recurrent ankle sprain is high and leads to further ligamentous damage as well as damage to the mechanoreceptors. Patients with repetitive ankle trauma are more susceptible to degenerative changes^[5].

As a result of the degenerative changes and a reduction in proprioceptive awareness, a correlation to postural instability may exist^[6], leading to a sense of

not being coordinated and a loss of movement control. In order for an ankle to have control, muscles and nerves must function synergistically. An altered sense of balance will heighten functional ankle instability because of increased movement at the body's periphery, away from the center of gravity^[7].

Dynamic posturography has become an important tool for understanding standing balance in clinical settings. The unilateral stance test quantifies postural sway velocity with the patient standing independently on either the right or left foot on the force platform, with eyes open and with eyes closed^[8]. Thus, the objective of this study was to identify quantitative postural sway assessed by unilateral stance test using computerized dynamic posturography in chronic ankle sprain athletes and normal subjects.

SUBJECTS AND METHODS

Twenty-six male athletes suffering from chronic ankle sprain and twenty-two healthy individuals as a control group matched for age and sex from the

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sports and balance clinics, were recruited for this study. Information from medical chart reviews was linked with survey data to create the database for the analyses. The diagnosis of chronic ankle sprain was made through a careful examination. X-rays of the ankle were done to rule out any bony pathology.

All the patients and the control group healthy individuals were evaluated clinically by musculoskeletal and neurological examination. Inclusion criterion for the trial included the ability to ambulate 25 feet independently. Exclusion criteria were the following: cognitive deficit; peripheral neuropathy; significant visual field defects; cerebellar or brain stem lesions; serious cardiac conditions; severe weight-bearing pain; and other serious organ and system disorders. After subjects passed the screening criteria, an informed consent was taken.

Computerized dynamic posturography¹⁸

All the subjects were evaluated clinically and tested by computerized dynamic posturography for the unilateral stance test. The unilateral stance test

quantifies postural sway velocity with the patient standing independently on either the right or left foot on the force platform, with eyes open and with eyes closed. The length of each trial was ten seconds.

Mean centre of gravity (COG) sway velocity (degree/second) which displays COG stability was taken while the patient stood independently on each leg with eyes open and with eyes closed. In Fig. 1 and 2, the center bar graph displays the percentage difference score of COG sway velocity with the bar pointing in the direction of the limb with the better performance. The shaded area on each graphic represents performance outside of the normative data range. Green bars indicate performance within the normal range; red bars indicate performance outside the normal range. A numerical value is given at the top of each bar.

Statistical analysis

Study data were analyzed using the SPSS (version 11.0) statistical package. The Student's "t" test indicates the magnitude of the difference of means and therefore, the magnitude of the observation. A

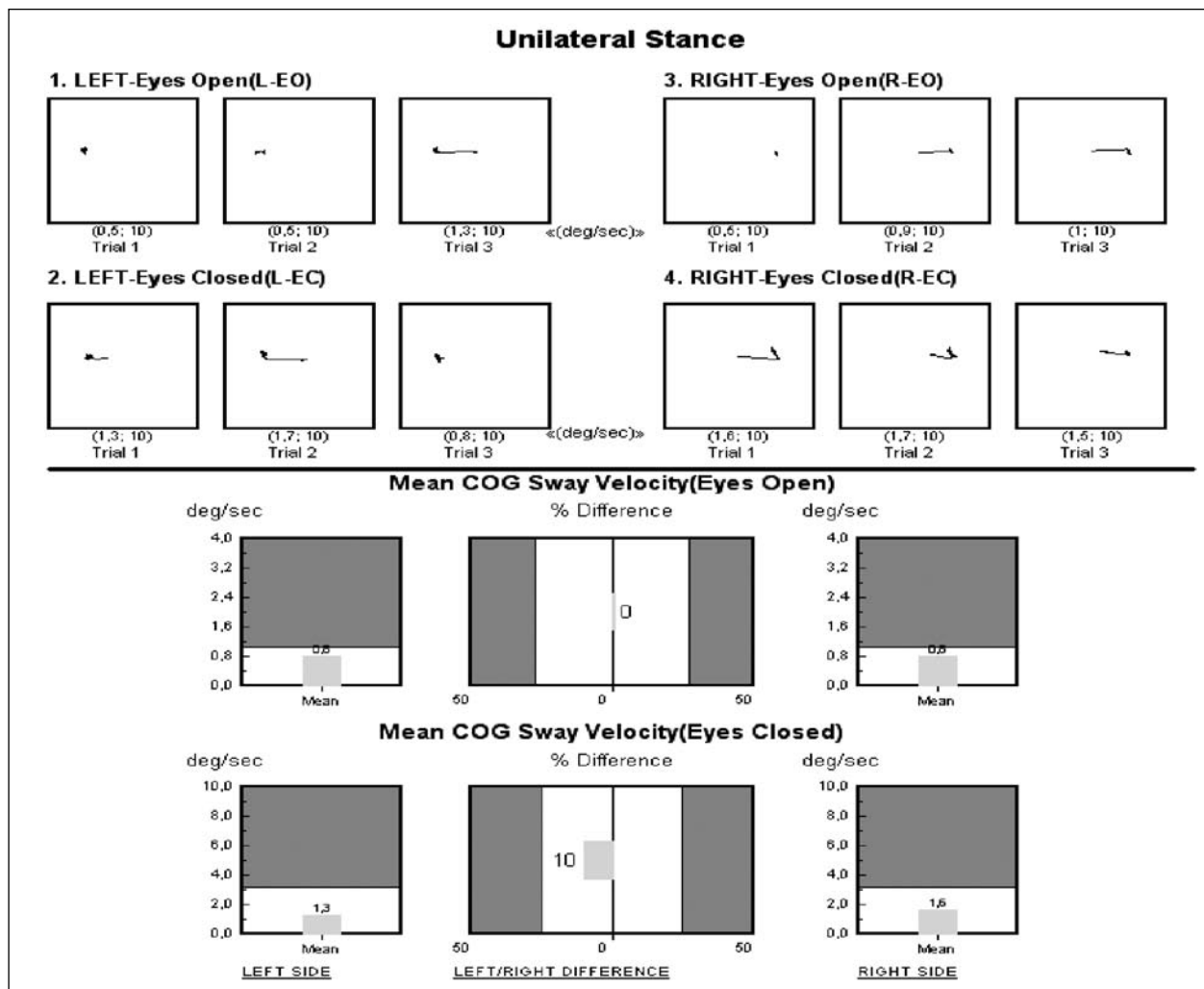


Fig. 1: Represents normal unilateral stance test of dynamic posturography

p-value of < 0.05 was used as significant^[9]. Linear regression (r-) correlation was also used to assess correlation between mean \pm SD of the percentage difference score of COG sway velocity during standing on left and right foot with eyes open and mean \pm SD of the percentage difference score of COG sway velocity during standing on left and right foot with eyes closed of unilateral stance test in 26 cases of athletes with chronic ankle sprain^[9].

RESULTS

Table 1 shows demographic and clinical data in 26 male athletes with chronic ankle sprain and 22 male healthy controls. The most frequently clinical findings of chronic ankle sprain were ankle pain (61.6%), tenderness (69.2%), swelling (53.8%), antalgic gait (34.6%) and inability to stand on tiptoes (26.9%). Fig. 1 represents normal unilateral stance test of dynamic posturography. Fig. 2 represents abnormal unilateral stance test of dynamic posturography.

Table 2 and Fig. 3 represent mean (\pm SD) parameters of the unilateral stance test of CDP in 26 male athletes with chronic ankle sprain and 22 controls. The unilateral stance test showed a significant increase of mean (\pm SD) COG sway velocity on left or right leg standing with eyes open and eye closed of athletes with chronic ankle sprain as compared to control group ($p < 0.05$). Also, there was a significant increase of mean (\pm SD)

Table 1: Mean (\pm SD) of demographic and clinical data in 26 male athletes with chronic ankle sprain and 22 healthy male volunteers

Data	Athletes with chronic ankle sprain n (%)	Control
Age (years)	23.1 \pm 3.9	22.0 \pm 2.7
Duration(months)	7.5 \pm 2.4	-
Causes of lesion		
Football	15 (57.6)	-
Basketball	5 (19.4)	-
Volleyball	4 (15.4)	-
Others	2 (7.6)	-
Site of lesion		
Right	16 (61.6)	-
Left	7 (26.9)	-
Bilateral	3 (11.5)	-
Pain of ankle	16 (61.6)	-
Tenderness of ankle	18 (69.2)	-
Swelling of ankle	14 (53.8)	-
Limp	9 (34.6)	-
Inability to stand on tiptoes	7 (26.9)	-

percentage difference score of COG sway velocity during standing on left and right foot with eyes open and eyes closed in athletes with chronic ankle sprain as compared to control group ($p < 0.001$).

In Table 3 and Fig. 4, we found direct significant (r-) correlation between mean (\pm SD) percentage

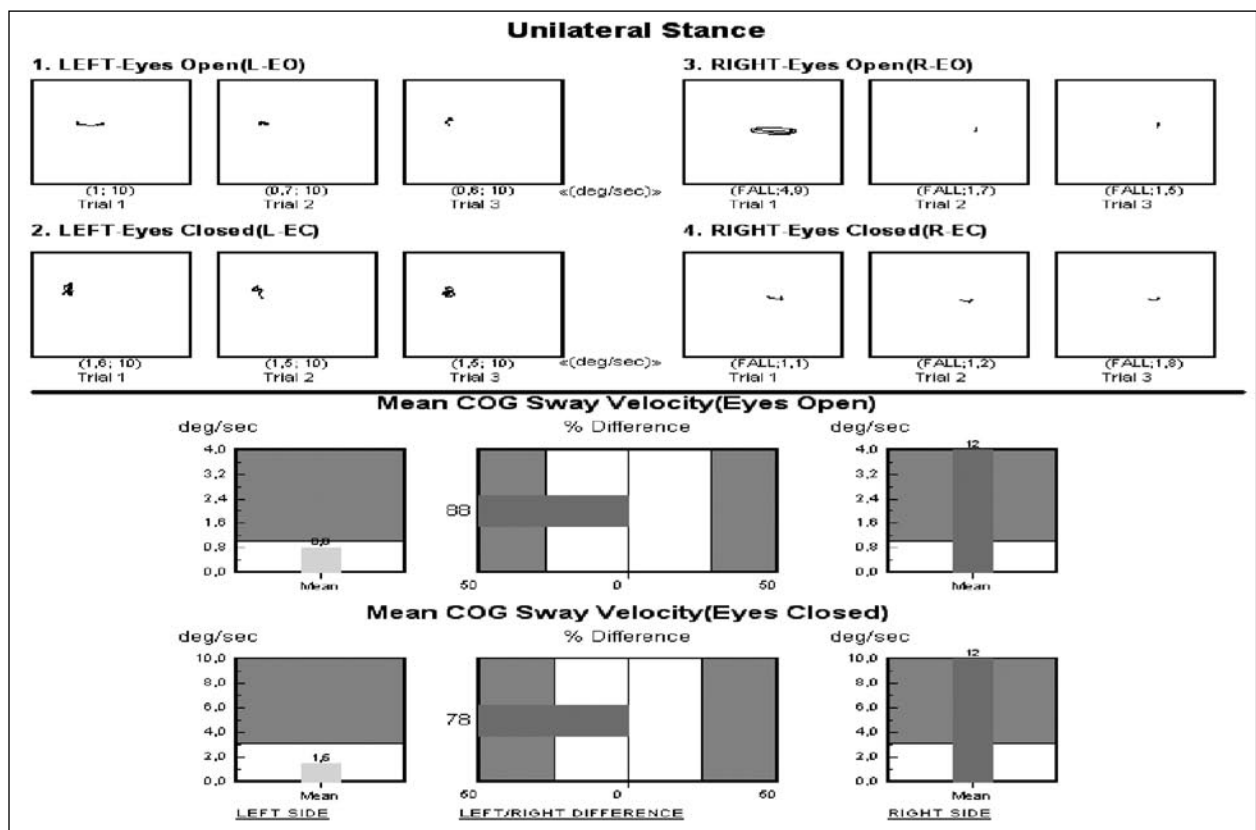


Fig. 2: Represents abnormal unilateral stance test of dynamic posturography

Table 2: Mean (\pm SD) of parameters of the unilateral stance test with eyes open and eyes closed in athletes with chronic ankle sprain and controls

Parameters of unilateral stance test mean (\pm SD)	Athletes with chronic ankle sprain	Control
Parameters of unilateral stance with eyes open		
1. Mean COG sway velocity during standing on left foot with eyes open (deg / sec)	2.12 \pm 0.63	0.69 \pm 0.22*
2. Mean COG sway velocity during standing on right foot with eyes open (deg / sec)	3.43 \pm 2.56	1.5 \pm 0.2 *
3. Mean \pm SD of the percentage difference score of COG sway velocity during standing on left and right foot with eyes open	28.7 \pm 14.9	2.4 \pm 0.5**
Parameters of unilateral stance with eyes closed		
1. Mean COG sway velocity during standing on left foot with eyes closed (deg / sec)	3.79 \pm 1.22	1.59 \pm 0.22*
2. Mean COG sway velocity during standing on right foot with eyes closed (deg / sec)	3.87 \pm 3.02	1.24 \pm 0.37 *
3. Mean \pm SD of the percentage difference score of COG sway velocity during standing on left and right foot with eyes closed	32.9 \pm 15.8	7.2 \pm 1.0**

Mean COG(central of gravity) sway velocity. Significant $p < 0.05^*$. Highly significant $p < 0.001^{**}$

difference score of COG sway velocity during standing on left and right foot with eyes open and mean (\pm SD) of the percentage difference score of COG sway velocity during standing on left and right foot with eyes closed of unilateral stance test in athletes with chronic ankle sprain ($r = 0.522$, $p < 0.001$).

DISCUSSION

The ankle sprains are among the most common injuries seen in physically active populations^[10]. Injuries to the lateral ligaments of the ankle complex are among the most common injuries incurred by athletes^[11]. Participation in athletic activity often leads to increased susceptibility to ankle sprains, and injuries that persist lead to repeated ankle sprains^[12]. Chronic ankle instability, sometimes associated with multiple ankle sprains, can lead to difficulty with walking, running and jumping^[13]. Previous research has also indicated that lateral ankle sprains are not isolated incidents; 40 to 75% of individuals who sprain their lateral ankle

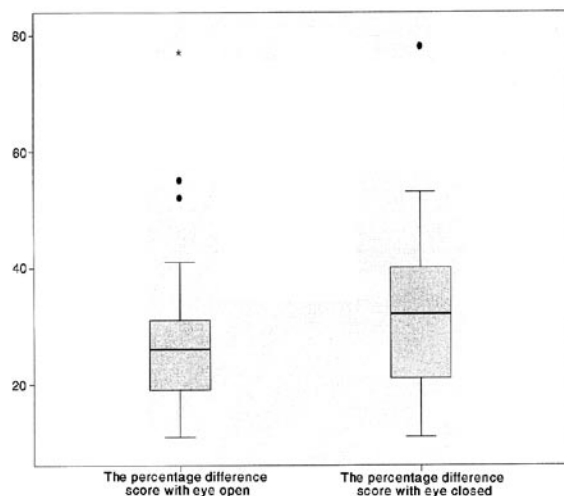
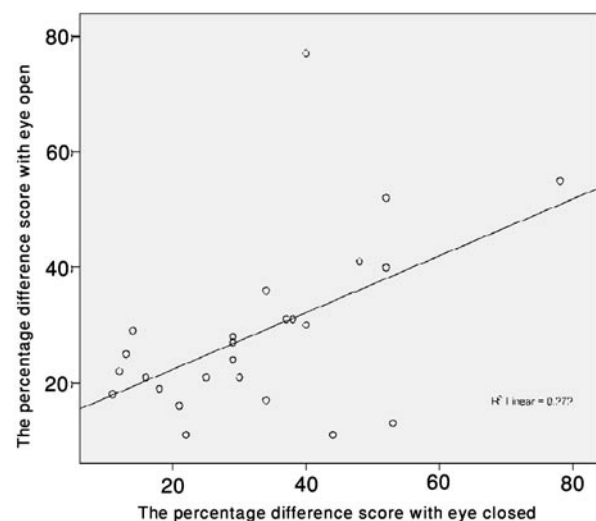
Table 3: Linear regression (r-) correlation between mean (\pm SD) of the percentage difference score with eyes open and mean (\pm SD) of the percentage difference score with eyes closed of unilateral stance test in athletes with chronic ankle sprain

Mean (\pm SD)	Mean (\pm SD) of the percentage difference score with eyes open
Mean (\pm SD) of the percentage difference score with eyes closed	A direct significant correlation ($r = 0.522$; $p < 001$) **

Highly significant $p < 0.001^{**}$

ligaments will develop chronic ankle instability^[13]. Upto 56.8% individuals do not seek medical treatment after suffering a lateral ankle sprain^[14].

In our study, the most frequent clinical findings in chronic ankle sprain were ankle pain (61.6%), tenderness (69.2%), swelling (53.8%), antalgic gait (34.6%) and inability to stand on tiptoes (26.9%). The

**Fig. 3:** Box plots showing mean (\pm SD) of the percentage difference score with eyes open and mean (\pm SD) of the percentage difference score with eyes closed in athletes with chronic ankle sprain**Fig. 4:** Scatter diagram of linear regression (r-) correlation between mean (\pm SD) of the percentage difference score eyes open and mean (\pm SD) of the percentage difference score with eyes closed in athletes with chronic ankle sprain ($r = 0.522$, $p < 0.001$).

unilateral stance test showed a significant increase of mean (\pm SD) COG sway velocity on left or right leg standing with eyes open and eye closed in athletes with chronic ankle sprain as compared to control group ($p < 0.05$). Moreover, there was a significant increase of mean (\pm SD) percentage difference score with eyes open and eyes closed in athletes with chronic ankle sprain as compared to control group ($p < 0.001$).

According to the National Collegiate Athletic Association^[15], ankle sprains are the most common injuries in men and women who participate in soccer, basketball, and volleyball. Most ankle sprains are inversion injuries that damage the lateral ligaments of the ankle^[16]. Upto 73% of individuals who sprain their ankles have residual symptoms including pain, repeated sprains, and episodes of "giving way"^[17]. A previous study found that after an ankle sprain, up to 40% of patients continued to report residual disability^[18] which might be persistent for seven years after inversion trauma^[19].

Our results are in agreement with various other studies which revealed increased postural instability after ankle injury. In addition, other authors^[20-22] have found an increase in various objective measures of postural control including measurements of center-of-pressure excursion length (LEN), root mean square velocity (VEL), and excursion range (RANGE) in injured limbs versus contralateral uninjured limbs after ankle sprain^[20].

Golomer *et al*^[21] demonstrated significant impairments of various objective measures of postural control including measurements of LEN and VEL, in injured limbs compared with uninjured limbs among five subjects between 4 - 15 days after ankle sprain. Leanderson *et al*^[22] showed significant increases in COP excursion variables in injured limbs compared with uninjured limbs among six ballet dancers within two weeks of experiencing ankle sprain. Each of these six injured dancers' postural control scores returned to preinjury levels with structured rehabilitation.

Hertel *et al*^[14] demonstrated a significant impairment in postural control after ankle sprain. Measurements of impaired postural control including LEN, VEL, and RANGE were elevated in injured limbs versus uninjured limbs in the frontal plane and in the sagittal plane. Orteza *et al*^[23] demonstrated impaired balance on a testing device similar to that of Golomer *et al*^[21] among subjects of ankle sprain compared with a group of healthy controls. Guskiewicz and Perrin^[24] demonstrated impaired postural control of ankle sprain among injured limbs compared with the limbs of healthy controls. Poor postural stability has also been reported to predispose physically active individuals to ankle sprains^[25].

However, our results are in contrast to some previous studies such as Bernier *et al*^[26] which did not

find significant difference in postural sway between patients with ankle instability and control group. Tropp *et al*^[27] found that mechanically unstable ankles did not show a decreased ability to maintain postural stability when measured with stabilometry under static conditions. One possible explanation of differences with other authors may be the method of subject recruitment and techniques.

The potential explanation for the deficits in postural control after ankle sprain in our results may be due to several factors. Freeman *et al*^[28] originally hypothesized that balance impairments after ankle sprain were the result of impaired proprioception due to damage to joint mechanoreceptors and afferent nerve fibers, which occurs in conjunction with ligamentous damage during hyperinversion. Impaired proprioception may cause diminished or delayed muscle response that provide dynamic stability to the ankle joint resulting in inadequate corrections to postural perturbations^[29-30].

Another explanation of impaired postural control might be due to altered proximal muscle activity in response to ankle injury. Subjects with ankle injuries have been shown to shift from the typical ankle strategy of balance maintenance during single leg stance to the less efficient hip strategy of balance^[31-32]. Another potential cause of impaired postural control after lateral ankle sprain is that lateral ligamentous injury may result in mechanical instability of the subtalar and talocrural joints and allow greater ranges of pronation and supination to occur during single-leg stance, thus resulting in greater magnitude and velocity of center-of-pressure (COP) excursions^[21-24].

CONCLUSION

This study represents the first attempt to use the dynamic posturography equipment as a diagnostic tool in assessment of impaired postural control in athletes with ankle sprain in Kuwait. Our study identifies quantifiably the impairment in postural control that might help to predict which athletes are predisposed to develop long-standing functional instability after ankle sprain injury.

The chronic ankle sprain has higher than normal COG sway velocity and impaired postural control. The ligamentous damage, ankle muscle strength deficits and proprioception deficits at the ankle joint may explain poor balance in ankle sprain. Future researches should include the effect of rehabilitation programs on single-leg stance in chronic ankle sprain.

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Original Article

Inducible Clindamycin Resistance in *Staphylococcus Aureus*: A Study from a Tertiary Care Hospital of North India

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ABSTRACT

Objectives: Clindamycin is a preferred therapeutic option in erythromycin resistant *Staphylococcus aureus* skin and soft tissue infections. However, a major concern regarding its use for staphylococcal infections is the possible presence of inducible resistance to clindamycin. The present study was aimed to determine the incidence of constitutive and inducible clindamycin resistance in *S.aureus* isolates in our hospital.

Design: Retrospective study

Setting: Pt. BDS University of Health Sciences, Rohtak, Haryana, India

Subjects: A total of 250 consecutive, non-duplicate *S.aureus* strains were isolated from various clinical specimens, both from inpatients and outpatients.

Interventions: Antibiotic susceptibility tests were performed using Kirby-Bauer disc diffusion method. Methicillin resistance was detected by oxacillin disc on Mueller-Hinton Agar (MHA) plate supplemented with 2%

NaCl. D-test was performed on all erythromycin-resistant and clindamycin-sensitive isolates to detect inducible clindamycin resistance.

Main Outcome Measures: Observed and counted were methicillin resistance in *S.aureus*, constitutive and inducible resistance of the isolates to clindamycin, origin of the MLSBi isolates that is "community" or "hospital" and resistance of MLSBi isolates to other drugs.

Results: Among 250 *S.aureus* strains, 112 (44.8%) were found to be Methicillin-resistant *Staphylococcus aureus* (MRSA) and 20% had MLSBi phenotype. MRSA isolates showed higher inducible as well as constitutive resistance ($p < 0.0001$) to clindamycin as compared to methicillin-sensitive *S.aureus* (MSSA). All *S.aureus* isolates having MLSBi phenotype were sensitive to vancomycin and linezolid.

Conclusions: The study strongly recommends the routine testing of *in vitro* inducible clindamycin resistance in *S.aureus* isolates as it will help in guiding therapy.

KEY WORDS: erythromycin, D-test, lincosamide, MLSBi phenotype

INTRODUCTION

The increasing incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections and changing patterns in antimicrobial resistance have led to renewed interest in the use of macrolide-lincosamide-group B streptogramin (MLSB) antibiotics to treat such infections^[1]. The MLSB antibiotics are chemically distinct but exert similar action by binding to 50S ribosomal subunit inhibiting bacterial protein synthesis^[2]. Macrolide resistance in staphylococci may be due to an active efflux mechanism encoded by *msrA* gene (conferring resistance to macrolides and group B streptogramins only) or may be due to ribosomal target modification, mediated *via* *erm* gene, which encodes enzymes that confer inducible or constitutive resistance to MLSB agents (MLSB resistance). In constitutive MLSB resistance, rRNA methylase is always produced, compared to inducible

MLSB resistance where methylase is produced only in the presence of an effective inducer^[3,4]. *In vitro*, *S. aureus* isolates with constitutive resistance (MLSBc strains) are resistant to erythromycin and clindamycin, while, isolates with inducible resistance (MLSBi strains) are resistant to erythromycin but appear susceptible to clindamycin. Failure to identify MLSBi resistance may lead to clinical failure of clindamycin therapy due to selection of constitutive *erm* mutants^[5]. This inducible MLSB resistance is not recognized by using standard susceptibility test methods, including standard broth - based or agar dilution susceptibility tests. However, it can be detected by a simple disc approximation test (D-test) by placing erythromycin (inducer) and clindamycin discs in adjacent positions. Flattening or blunting of the zone around clindamycin disc adjacent to erythromycin disc indicates the presence of inducible resistance to clindamycin^[3].

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In the present study, the aim was to determine the incidence of methicillin resistance among *S.aureus* isolates from various clinical samples and to detect inducible MLSB resistant strains. Also, we tried to ascertain the relationship between MRSA and MLSBi isolates, association of MLSBi isolates with community or nosocomial setting and lastly, treatment options for these MLSBi isolates.

MATERIALS AND METHODS

Bacterial isolates

This study included 250 consecutive, non-duplicate strains of *Staphylococcus aureus* isolated from various clinical specimens (pus, wound swabs, blood, respiratory tract, urine, high vaginal swabs and body fluids), derived from both outpatients and inpatients of our teaching and tertiary care hospital during March 2007- July 2008. *S.aureus* isolates were identified using standard microbiological procedures^[6].

Detection of methicillin resistance

All identified isolates of *S. aureus* were subjected to antibiotic susceptibility testing by Kirby-Bauer disc diffusion method based on guidelines from the Clinical Laboratory Standards Institute (CLSI)^[7]. Methicillin resistance was detected by using oxacillin (1 μ g) disc on a swab inoculated Mueller-Hinton Agar (MHA) plate supplemented with 2% NaCl and incubating at 35 °C for 24 hours^[8].

Detection of inducible clindamycin resistance

Inducible clindamycin resistance was detected by performing a disc approximation test, by placing a 2 μ g clindamycin disc at a distance of 15 mm (edge to edge) from a 15 μ g-erythromycin disc on the same plate as a part of the normal disc diffusion procedure^[9]. All antibiotic discs used in the study were procured from Hi-media® Laboratories, Mumbai, India. *S.aureus* American Type Culture Collection (ATCC) 25923 was used to achieve quality control (QC) for antibiotic sensitivity tests. Additional QC was performed with separate in-house selected *S.aureus* strains that demonstrated positive and negative D-test reactions.

Reporting

Interpretation was done in accordance with CLSI guidelines. Isolates resistant to both erythromycin and clindamycin were defined as showing constitutive MLSB resistance (MLSBc phenotype). Those showing flattening or blunting of the clindamycin zone adjacent to the erythromycin disc (referred to as a "D" zone) were defined as having inducible clindamycin resistance (MLSBi phenotype), and those that were resistant to erythromycin and sensitive to clindamycin (no induction) were defined as showing the MS phenotype^[9].

All strains with MLSBi phenotype were then tested for antimicrobial susceptibility using Kirby-Bauer disc diffusion method for the following antimicrobial agents with their disc content in brackets:- cephalexin (30 μ g), amoxicillin / clavulanic acid (20 / 10 μ g), trimethoprim / sulfamethoxazole (1.25 / 23.75 μ g), linezolid (30 μ g), vancomycin (30 μ g), doxycycline (30 μ g), quinupristin-dalfopristin (15 μ g), ciprofloxacin (5 μ g) and gatifloxacin (5 μ g).

Statistical analysis

The results obtained were analyzed statistically using Chi-square test to compare differences between groups. All analyses were two tailed, and $p < 0.05$ was considered significant.

RESULTS

Among 250 *S.aureus* isolates studied, maximum isolation was from pus and pus swabs (60.8%), followed by blood (14.8%). The rate of isolation from inpatients was 69.2%. 44.8% isolates were found to be MRSA. Table 1 shows the distribution of MLSB resistance phenotypes (constitutive resistance, inducible resistance and MS phenotype) among MRSA and MSSA isolates.

A total of 50 (20%) isolates of *S.aureus* were found to be D-test positive. Among MRSA isolates, 44.7% had the constitutive and 33.9% had the inducible clindamycin resistance. In MSSA isolates, 11.6% and 8.7% isolates exhibited the constitutive and inducible resistance phenotypes respectively. Thus, both the constitutive and inducible resistance phenotypes were found to be significantly higher in MRSA isolates compared to MSSA ($p < 0.0001$ and $p < 0.0001$ respectively by Chi-square test). Isolates with MS phenotype and sensitive to both erythromycin and clindamycin were predominant among MSSA.

Also, we found that out of 38 MRSA strains which had MLSBi phenotype, 24 (63.2%) were hospital-acquired and 14 strains (36.2%) were community-acquired. Similarly, among 12 MSSA strains with MLSBi phenotype, hospital-acquired strains (66.7%) were more as compared to community-acquired (33.3%).

Susceptibility of the isolates with MLSBi resistance was cephalexin 48%, amoxyclav 44%, cotrimoxazole 24%, doxycycline 46%, quinopristin-dalfopristin 54%, ciprofloxacin 44%, gatifloxacin 64%, vancomycin 100% and linezolid 100%.

DISCUSSION

Clindamycin is a useful drug in the treatment of skin and soft-tissue infections and serious infections caused by staphylococcal species, as well as anaerobes. It has excellent tissue penetration (except for the central nervous system), accumulates in abscesses, and no renal

Table 1: Distribution of MLSB resistance phenotypes among MRSA and MSSA isolates

Isolates (n)	MLSBc phenotype (%)	MLSBi phenotype (%)	MS phenotype (%)	Sensitive to both ERY and CLI (%)
MRSA (112)	50 (44.7)	38 (33.9)	11 (9.8)	13 (11.6)
MSSA (138)	16 (11.6)	12 (8.7)	27 (19.6)	83 (60.1)
Total (250)	66 (26.4)	50 (20.0)	38 (15.2)	96 (38.4)

MRSA – Methicillin - resistant *S.aureus*, MSSA- Methicillin - sensitive *S.aureus*, MLSBc - Constitutive MLSB resistance, MLSBi - Inducible clindamycin resistance, MS phenotype - Resistant to erythromycin and sensitive to clindamycin but no induction, ERY- Erythromycin, CLI-Clindamycin

dosing adjustments are needed. Good oral absorption makes it an important option in outpatient therapy or as follow-up after intravenous therapy. Clindamycin is also of particular importance as an alternative antibiotic in the penicillin-allergic patient^[3].

For any clinical microbiology laboratory, the differentiation of erm-mediated inducible MLSB (MLSBi phenotype) isolates from isolates with msrA-mediated (MS phenotype) resistance is a critical issue because of the therapeutic implications of using clindamycin to treat a patient with an inducible clindamycin-resistant *S.aureus* isolate^[5]. Since the MLSBi resistance mechanism is not recognized by using standard susceptibility test methods and its prevalence varies according to geographic location, D-test becomes an imperative part of routine antimicrobial susceptibility test for all clinical isolates of *S.aureus*. Failure to identify MLSBi resistance may lead to clinical failure of clindamycin therapy. Conversely, labeling all erythromycin-resistant staphylococci as clindamycin-resistant prevents the use of clindamycin in infections caused by truly clindamycin-sensitive staphylococcal isolates. Hence, CLSI recommends routine testing of all staphylococcal isolates for MLSBi resistance^[1,3].

In our study, we found that among 112 MRSA isolates, 44.7, 33.9 and 9.8% isolates had the constitutive MLSB resistance, inducible clindamycin resistance and the MS phenotype respectively. Both constitutive and inducible resistance was significantly higher in MRSA isolates in comparison to MSSA. These findings are in concordance with various studies reported by Azap *et al*, Schmitz *et al*, Fiebelkorn *et al*, and many more^[2,3,10-14]. Likewise, from India, Gadepalli *et al*, Gupta *et al*, and Pal *et al* had similar findings^[1,15,16]. Schreckenberger *et al*^[17] and Levin *et al*^[18] showed higher percentage of inducible resistance in MSSA as compared to MRSA which is contrary to our study. None of the above quoted studies found MS phenotype among MRSA isolates except those by Gupta *et al* and Pal *et al*^[15,16] which is in accordance with our study. Similarly, Angel *et al* from India found that among the MRSA isolates 12% had the MS phenotype^[19]. In our study, we found that among MSSA isolates, MS phenotype was predominant (19.6%), with 11.6 and 8.7% isolates having MLSBc and MLSBi resistance respectively. On

the contrary, Deotale *et al* reported that only 1.6% of MSSA isolates had MLSBi phenotype and Gupta *et al* reported high level of inducible resistance (17.3%) compared to constitutive resistance (10%) in MSSA isolates^[15,20]. However, Angel *et al* and Ciraj *et al* did not find constitutive MLSB resistance pattern in MSSA isolates^[19,21]. Possible variations in the prevalence of constitutive, inducible clindamycin resistance and MS phenotype could be explained due to differences in bacterial susceptibility in different geographical areas and also due to varying antimicrobial prescribing patterns of physicians. These differences highlight the significance of inducible clindamycin resistance in our geographical setting.

The presence of a higher rate of inducible clindamycin resistance in hospital-acquired strains (36 isolates out of 50) is also a critical finding in the study. This is explained by the fact that nosocomial strains are often multi-drug resistant owing to injudicious use of all available effective antimicrobial agents. Also, low prevalence of MLSBi in community setting makes clindamycin a good therapeutic option.

The treatment options recommended for serious infections due to MRSA are the glycopeptide antibiotics such as vancomycin or teicoplanin, linezolid, quinupristin-dalfopristin, trimethoprim-sulfamethoxazole, clindamycin, doxycycline, fluoroquinolones or rifampicin^[22]. In our study, we did not find any isolate showing resistance either to vancomycin or to linezolid. Recent reports of *S. aureus* isolates with intermediate or complete resistance to vancomycin portend a chemotherapeutic era in which effective bactericidal antibiotics against this organism may no longer be readily available. Clindamycin is a useful drug and is usually advocated in severe in-patient MRSA infections depending upon the antimicrobial susceptibility results^[22]. Further, by using clindamycin, use of vancomycin can be avoided. However, expression of inducible resistance to clindamycin could limit the effectiveness of this drug. Hence, clinical laboratories should report *in vitro* inducible clindamycin resistance in *S. aureus* isolates and clinicians should be aware of the potential of clindamycin treatment failure in patients with infections caused by inducible resistant strains. In such cases, vancomycin and linezolid are the drugs which are considered for therapy^[1].

CONCLUSION

The present study highlights a fairly high incidence of inducible clindamycin resistance from both the hospital as well as community in this geographical area. Use of an easy to perform and reliable D-test for its detection is strongly advocated in the routine protocol of clinical microbiological laboratories. This will offer great help to clinicians regarding the accurate use of this anti-staphylococcal drug for therapy especially in skin and soft tissue infections caused by macrolide resistant isolates.

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Original Article

Allergenicity to Allergens like *Prosopis Juliflor* and Date Tree Pollens in Saudi Arabia

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ABSTRACT

Objective: To determine the major causes of allergic reactions and the level of sensitivity to local allergens among residents of Saudi Arabia

Design: Retrospective data analysis

Setting: National Center for Allergy, Asthma and Immunology, Riyadh, Saudi Arabia

Subjects: A total of 110 patients who had allergies underwent skin testing. Twelve allergens were used for this study including the most commonly reported allergen *Prosopis juliflora* (mesquite) pollen.

Intervention: Skin prick tests

Main Outcome Measures: Date tree pollens and *prosopis*

Results: Among the causes of allergies found in the 110 patients who were tested, 75.5% were found to be positive to

prosopis, 59% to date tree pollens and 54.5% reacted to both. Positive reactions to CAT epithelium (46.4%), Bermuda grass (66.4%), Russian Thistle (71%) and Atriplex should also be considered as major factors causing sensitization in the region as this can also cause cross-reactivity among tree pollens and not necessarily to *prosopis* pollen.

Conclusion: The findings suggest that *prosopis* pollen is a sensitizing factor to allergic patients in Saudi Arabia. The significance of the human allergens of mesquite and their possible cross-reactivities with other tree pollens, merit further research (a) to draw conclusions of *prosopis*-hypersensitivity in many multiple sensitive patients and (b) to consider *Prosopis* as one of the major allergens in Saudi Arabia.

KEY WORDS: allergy, *Phoenix dactylifera*, *Prosopis juliflora***INTRODUCTION**

It has been observed that there is an increasing occurrence of allergic diseases in Saudi Arabia in the last few years^[1]. Among those reported factors, increase in vegetation and introduction of new plants were most significant, the most common of which is *Prosopis juliflora*. There have been reports from a few countries including the Arabian States^[2-4], Kuwait^[5], India^[6-8] and South Africa^[9] of hypersensitivity to *Prosopis Juliflora* pollen antigen. *Prosopis* is a genus of flowering plants belonging to the pea family, Fabaceae. It contains around 45 species of spiny trees and shrubs found in subtropical and tropical regions of the Americas, Africa, Western Asia, and South Asia. They often flourish in excessively dry soil and are resistant to drought, on occasion developing extremely deep root systems. Several species of *prosopis* were introduced as roadside decoration in Saudi Arabia.

Among the reported species of *prosopis*, nine are known to be present in Saudi Arabia which includes *Prosopis juliflora*, also known as mesquite. Large amounts of pollen debris from *Prosopis juliflora* that

are deposited below the trees as it blooms four times a year in the region, can be easily distributed through vehicular, human and animal movements. As indicated in published data from different countries, *prosopis* pollen which are pollinated partly through insects can become airborne^[3,5,7].

Another species that was used in this study is *Phoenix dactylifera* commonly known as the date palm, which belongs to the genus *Phoenix* and is extensively cultivated for its edible sweet fruit. Dates are naturally wind pollinated but in both traditional oasis horticulture and in the modern commercial orchards they are entirely pollinated manually^[10].

Because airborne pollen is carried for long distances, it does little good to rid an area of an offending plant--the pollen can drift in from many miles away and many never reach their targets. Instead, they enter human noses and throats, which can result in sensitization of susceptible people and subsequently bring about symptoms of respiratory allergic diseases. Allergies to pollens can also develop sensitivities to other irritants like dust and mould.

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Despite the fact that international studies on *Prosopis* induced allergenicity are very limited, the studies published^[2-9] from a few countries strongly suggest the allergenic role of airborne *Prosopis* pollen. However, the current study is the first detailed report on *Prosopis* allergenicity in Saudi Arabia. As such, it provides a basis for future biochemical and immunological investigations on *Prosopis*-induced asthma and allergies in the region. The purpose of this study was to determine the sensitization level of individuals to local allergens specifically to *Prosopis juliflora* and date palm pollens.

PATIENTS AND METHODS

Patients

The present study was conducted for a period of one year from January 2009 to February 2010. During this period patients with allergic diseases coming to National Centre for Allergy, Asthma and Immunology, Riyadh, were screened by skin prick tests for different allergens.

A total of 110 patients (ages ranging from 5 – 77 years) sufferings from different symptoms of allergies (like asthma, allergic rhinitis and food allergy) were evaluated. The patient's average age was 23 years with median of 18 ± 14.69 years. There were 62 adults (56.4%) and 48 (43.6%) children. Out of the 110 patients, 71 were male (64.5%) and 39 were female (35.5%).

Allergens

In addition to *Prosopis juliflora* and *Phoenix dactylifera* (date) pollen extracts, there were ten other allergens used in the skin tests. The other allergens included were Cat epithelium (fel d1), *Cynodon*

dactylon (bermuda grass), *Phelum pratensis* (timothy grass), *Chenopodium album* (lamb's quarter-goose foot), Sage brush, English plantain, Russian thistle (salworth), Mugwort, Acacia mix and Wingscale (atriplex).

Skin Prick Test

Skin Prick Tests (SPT) were performed by competent personnel under the supervision of a physician. Antihistamine and / or related medication were removed prior to testing. The diluted extract of each allergen was applied to the patients' forearm using a standard lancet. Normal saline as negative control and histamine as positive control were also used. SPT results were read after 15 minutes and graded positive or negative according to a standard scale.

Statistical Analysis

Statistical analyses of data were performed using Microsoft Excel. All values were represented as mean \pm SD values.

RESULTS

The SPT results of patients allergic to mesquite (*Prosopis*) and date tree pollen extracts are shown in Fig. 1. About 75.5% of patients had positive reactions to mesquite (*Prosopis*), 59% to date tree pollens and 54.5% positive reactions to both pollen extracts. SPT results of the 110 patients allergic to all allergens applied aside from mesquite and date tree are shown in Fig. 2. Positive reactions to CAT epithelium (46.4%), Bermuda grass (66.4%), Russian thistle (71%) and Atriplex can also be considered major factors causing sensitization in the region.

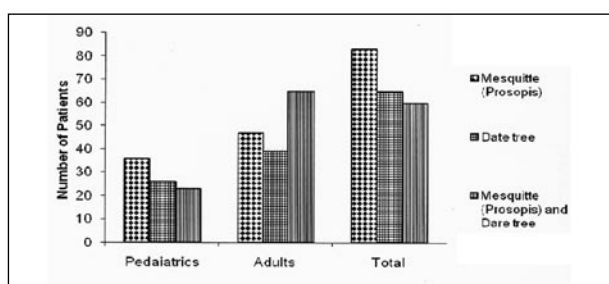


Fig. 1: Patients allergic to mesquite (*Prosopis*) and /or date tree

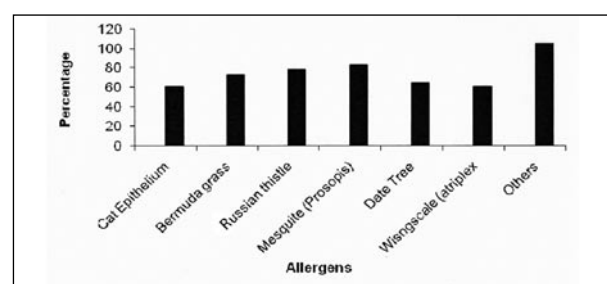


Fig.2: Positive SPT results to various allergens in 110 patients

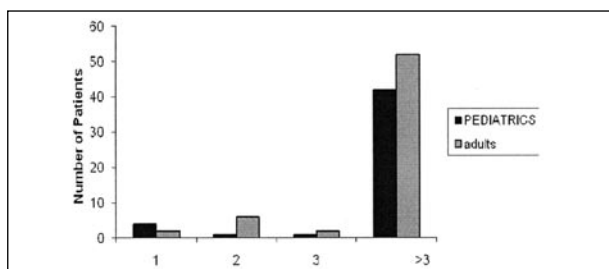


Fig. 3: Patients allergic to one or more allergens

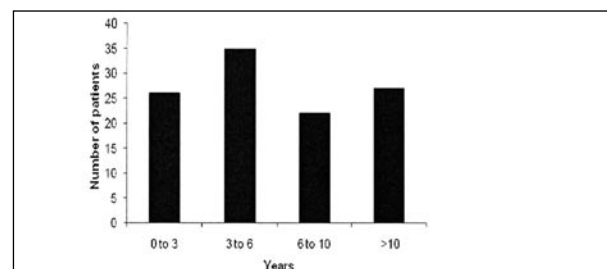


Fig. 4: Duration of symptoms

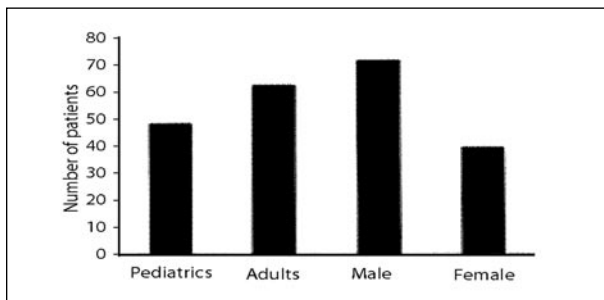


Fig. 5: Population distribution according to age & sex

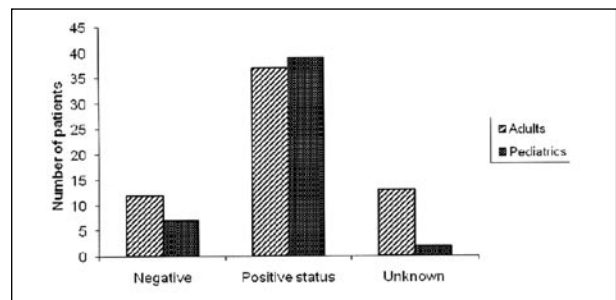


Fig. 6: Family history of allergic patients in relation to age

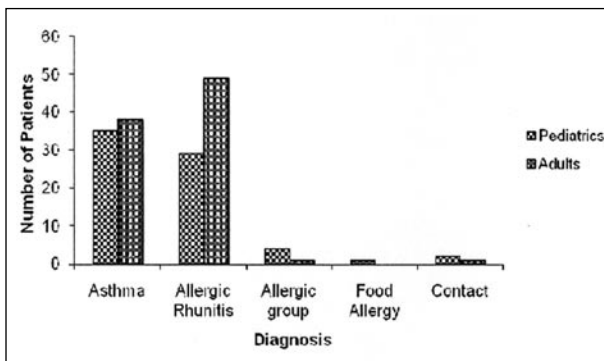


Fig. 7: Diagnosis in relation to age

Fig. 3 shows the number of patients who had positive reactions to more than one allergen. This data shows the possibility of cross-reaction of one allergen with other pollen sensitization like *Prosopis* and / or date tree. The degree of allergic reaction in relation to age group of patients tested is presented in Fig. 4. The severe positive reaction of allergens was noted in the age group 3 - 6 yrs old (31.8%) and moderate for the age group 0 - 3 yrs (23.6%) and > 10 yrs (24.5%). Mild reactions were seen in age group 6 - 10 yrs (20%). Fig. 5 shows the distribution of patients according to age and sex. Out of 110 patients, 46% were children and 55% were adults; 64% female and 37% male. Fig. 6 shows that most of the patients tested (both adults and children) had history of allergies. Fig. 7 shows that most of the patients diagnosed were positive for allergic rhinitis and asthma with adults having the most positive results.

DISCUSSION

To date, there are very limited studies reported on sensitization to *Prosopis*. However, international reports published from a few countries strongly suggest sensitivity factors to airborne *prosopis* pollen. As such, future researches or testing should be carried out on *Prosopis*-induced asthma and other allergies in the region.

Recently, *P. juliflora* pollen allergens (family: Leguminosae) with other tree species has also been delineated^[11], but efforts are required to investigate cross-allergenicity of foods and pollen belonging to the legume botanical family. This is also indicative of

availability of allergen sources (*Prosopis* pollen) and their impact and / or ability to induce allergic reaction in and around the region. This finding is supported by the work of Novey *et al*^[3], who trapped *Prosopis* pollen from a considerable distance from its source in California. Several common foods like chickpea, green gram, egg white, and bean fresh / red gram have been reported to cause allergenicity and concomitant sensitization in several patients^[12]. By conducting diagnostic tests on 100 consecutive patients using 30 pollen antigens, they obtained 42% positive on scratch test and an additional 20% positive intradermal test to *Prosopis* extracts. He concluded that mesquite pollen is a potent allergen capable of evoking immediate hypersensitivity reactions in a susceptible population remote from the plant source. Lucas and Buckley^[4] also studied the prevalence of epicutaneous flare reactions to allergenic pollen including mesquite, and concluded that it is mesquite which exhibits the most informative positive reaction.

The findings of this study revealed that (a) airborne pollen allergy is a major factor which can contribute to asthma and other respiratory diseases; (b) a higher positive reaction (75.5%) to *prosopis* in patients was noted using SPT diagnosis; (c) date tree pollen allergy might cross-react with *prosopis* (54.5%) as shown in SPT results; (d) other allergens which had positive SPT results should also be given attention like CAT epithelium (46.4%), bermuda grass (66.4%), Russian thistle (71%) and Atriplex which can also cause cross-reactivity among tree pollens and not necessarily to *prosopis* pollen.

The SPT results presented wherein a higher positive reaction to *Prosopis juliflora* extract were obtained, indicate that patients are sensitized with specific IgE

Table 1: Illustrates the standard scale of SPT

Saline / Histamine	Standard Scale
Saline/Glycerine	0
Histamine	3+
Same as histamine	3+
< histamine > Saline	
> histamine	2+ (1/2 histamine size)
Only ≥ is considered positive	4+

antibodies to *Prosopis juliflora*, where a higher level of these pollens maybe found. However, in a test conducted by Novey *et al*^[2], it was concluded that mesquite pollen is a potent allergen capable of causing immediate hypersensitivity reactions in a susceptible population remotely from the plant source. Sensitivity to one or more aeroallergens is common in patients, indicating high level of aeroallergen sensitization in patients with airway allergy residing in the Riyadh region^[13].

Some progress on the biochemical aspect of *Prosopis* allergen has been made, *e.g.*, *Prosopis juliflora* pollen allergen extract has been fractionated by sephadex (G-100 gel filtration)^[14]. Six different fractions were obtained, which were confirmed by sodium dodecyl sulphate polyacrylamide gel electrophoresis^[15]. A fraction called E (MW 20,000 kd) consisted mainly of allergenic molecules^[16,17]. However, it appears that no other species of *Prosopis* has been studied in relation to antigenic properties or compared with *Prosopis juliflora*. Consequently, characterized and purified antigens from *Prosopis* spp., as per WHO reference, have not yet emerged. In addition, humoral and cellular cross-reactivity between *Prosopis* pollen and *Phaseolus* seed allergens has been shown recently^[17,18].

CONCLUSION

The findings documented suggest that *Prosopis* pollen is a sensitizing factor for allergic patients in Saudi Arabia, with a considerable number of positive reactions. As they are and will be introduced by the millions as roadside ornamentation individuals in these locations might be sensitized with *Prosopis juliflora*. The sensitizing effect may take place at any region where a higher level of this pollen may be found. However, further studies and / or investigation are needed to draw conclusions of *prosopis*-hypersensitivity in many multiple sensitive patients and we might consider *Prosopis* as one of the major allergens in Saudi Arabia.

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Original Article

Pregnancy Associated with Brucellosis and Acute Viral Hepatitis: Course and Outcome (Co-infections in Pregnancy)

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ABSTRACT

Objective: To assess the outcome and course of pregnancies complicated by Brucellosis (BCS) and acute viral hepatitis (AVH) infections

Design: Prospective study

Setting: Diyarbakir State Hospital, Turkey

Subjects: Eighty-eight pregnant women admitted to Diyarbakir State Hospital, Turkey

Intervention: Serum agglutination test (SAT), Coombs anti-Brucella test and / or blood culture system were used in the diagnosis of BCS. Enzyme-linked immunosorbent assays (ELISA) and polymerase chain reaction (PCR) was used in the diagnosis of viral hepatitis.

Main Outcome Measures: The clinical course and delivery pattern of 32 healthy pregnant women was compared with that of 32 pregnant women who had BCS and 24 pregnant women who were concurrently infected with BCS and AVH.

Results: There was no maternal mortality. Preterm delivery occurred in 18.75% of the 32 pregnant women with BCS and 37.5% of 24 pregnant women with BCS and AVH ($p = 0.004$). The incidence of low birth weight was also significant between the two groups ($p < 0.0001$). Antepartum hemorrhage might be a warning sign of the occurrence of complications in pregnant women with BCS and AVH ($p < 0.001$). An important observation from the present study is that maternal BCS and AVH (even concurrent) had no effect on the incidence of congenital malformations or stillbirths; it did increase the incidence of prematurity and low birth weight over that seen in the general delivery population.

Conclusion: In spite of the high complication rates, BCS and AVH in pregnancy are well-tolerated diseases even when they occur together.

KEY WORDS: acute viral hepatitis, brucellosis, pregnancy

INTRODUCTION

Brucellosis (BCS) is rare in pregnancy. There is controversy about the relationship between BCS and the outcome of pregnancy^[1]. In Turkey, BCS is common, especially in the Middle, East and Southeast Anatolia regions. According to reports from the Turkish Ministry of Health, 37 cases were reported in 1970, with numbers rising to 18,408 cases in 2004 (incidence rate 25.67 / 100,000)^[2]. According to some authors, it is thought that this increase is a result of improvements in diagnosis and increased reporting, rather than a real increase in the prevalence of the disease^[3].

Liver test abnormalities and jaundice are also rare in pregnant women and are seen in 0.3 - 3% of pregnancies^[4,5]. Acute viral hepatitis (AVH) is the most common cause of jaundice in pregnancy^[6-8]. Opinions differ over the maternal and fetal outcome of pregnancies associated with viral hepatitis.

The aim of this study was to answer some key questions regarding BCS and AVH during pregnancy and to investigate if the two endemic diseases occurring concurrently during pregnancy could change the normal course of pregnancy. The effect of antibrucellosis treatment in pregnancy was also assessed in the presence of liver dysfunction possibly caused by AVH.

SUBJECTS AND METHODS

Study settings

Diyarbakir is the largest city in Southeastern Turkey. Situated on the banks of the river Tigris, it is the administrative capital of Diyarbakir province, with a population of almost 1.5 million. Diyarbakir State Hospital is the biggest state hospital serving the region. We studied a total of 88 pregnant women admitted to Diyarbakir State Hospital from July 2003 to May 2010.

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Informed consent was obtained from all women who participated in the study.

The study was approved by the Local Health Directorate and Administrative Committee of the Diyarbakir State Hospital. The study protocol conforms to the ethical guidelines of the 1975 declaration of Helsinki.

Patient groups

We reviewed 32 healthy pregnant women (control group), 32 pregnant women with Brucella (group B) and 24 pregnant women infected with BCS and AVH concurrently (group B + AVH). All pregnant women were between 20 - 40 years of age and had no history of spontaneous abortion prior to the study period. None of the women had a history of blood transfusion.

Definitions

The reproductive outcomes of 88 pregnant women were followed for the period from July 2003 to May 2010. The first trimester of pregnancy was defined as a gestational age of 12 weeks or less, the second trimester as 12 to 24 weeks, and the third trimester as more than 24 weeks. Fetal death that occurred at less than 24 weeks of gestation was considered spontaneous abortion, while fetal death that occurred after 24 weeks of gestation was designated 'intrauterine fetal death'. Preterm delivery was defined as the birth of a baby before 37 weeks but after 24 weeks of gestation^[9].

Depending on the history, symptoms, and clinical presentation time, BCS patients were divided into three groups: acute (0 - 2 months), sub-acute (2 - 12 months), and chronic (> 12 months). Those who had been diagnosed with BCS previously and cured appropriately but whose clinical and laboratory findings had become positive again were regarded as having relapse^[9].

Serological testing

The diagnosis of BCS was based on serum standard tube agglutination test (SAT), Coombs anti-Brucella test and / or blood culture in the pregnant women whose clinical findings suggested BCS. SAT is performed by mixing dilutions of serum from 1 / 20 to 1 / 2560 with brucella antigen in test tubes. A seroconversion or a four-fold rise in SAT titer or the first serum obtained had a serum agglutination titer or a Coombs anti-Brucella test of $\geq 1 / 160$ or a positive growth of Brucella species in culture were accepted as diagnostic of BCS. All diagnostic blood cultures yielded Brucella melitensis as the causative agent. Brucella abortus 99S antigens of Cromatest (Refik Saydam Hifzissihha Ins, Turkey) were used for SAT. In cultures, Vitek 2 compact Instrumented Blood Culture System (Biomerieux Inc., France) was used.

All patients had a detailed history taken and underwent a thorough clinical examination. All patients were also evaluated by abdominal ultrasonography.

The serological markers of Anti-HAV IgM, HBsAg, hepatitis Be antigen (HBeAg), antibody to HBeAg (anti-HBe), antibody to hepatitis B core antigen IgM (anti-HBc-IgM), anti-HBs and antibody to hepatitis C virus (anti-HCV) were investigated in the presence of jaundice and abnormal liver biochemical tests. Commercial kits based on the enzyme-linked immunosorbent assay (ELISA) (E170, Roche, Germany) method were used in hepatitis B virus DNA (HBV-DNA) detection and polymerase chain reaction technique (PCR) was used in hepatitis C virus RNA (HCV-RNA) (ABI Prism 7700 Sequence Detection System- real time PCR, USA) detection at the Hifzissihha National Public Laboratories and / or Dicle University Medical Microbiology Laboratories.

Patient treatment and follow up

Pregnant women who had BCS were treated with one of four antibrucellosis treatment regimens. The regimens included: TMP-SMX (co-trimoxazole) or TMP-SMX / rifampicin or cephtriaxone / rifampicin or only rifampicin in addition to supportive therapy. The dose of the antibiotic regimens were as follows; rifampicin (600 mg/day po for 6 wk), intravenous cephtriaxone 2 g/day, co-trimoxazole (80 mg of TMP and 400 mg of SMZ every 12 hours). TMP-SMZ was not given in the 3rd trimester because of the risk of jaundice and kernicterus for the newborn. When required, the duration of therapy was extended and these data were recorded.

Pregnant women who participated in our study were followed up during pregnancy, the neonatal period and at least for six months after completing therapy. Antepartum antimicrobial treatment was given to all pregnant women with BCS. Outpatients were asked for control visits at two weekly intervals. After treatment, they were seen once a month. All patients had a detailed obstetric evaluation. During these control visits, hepatitis markers, SAT, biochemical tests, complete blood count, C reactive protein (CRP), urine test and erythrocyte sedimentation rate (ESR) were performed^[9]. These tests were repeated until full recovery. The cases were presumed cured, if they remained seronegative on at least three visits during the follow-up period. In all B + AVH pregnant women bed rest was offered and when the tested liver enzymes increased beyond normal values BCS treatment was stopped and was restarted after normalization.

Statistics

Statistical analysis was carried out using Stat Cal of Epi INFO 2000 software package (Center for Disease Control and Prevention, Atlanta, GA, USA) program. The chi-square test was used in the statistical analyses. Chi-square test was used to determine the relationship between categorical variables. A p-value of < 0.05 was considered statistically significant.

Table 1: Characteristics of B and B + AVH group in southeastern Turkey

Characteristics	Healthy pregnant Women (N = 32)	Pregnant women with Brucellosis (N = 32)	Pregnant women with B + AVH (N = 24)
	n	n (%)	n (%)
Age			
20 - 25	9	6 (18.75)	5 (20.8)
26 - 30	14	15 (46.8)	9 (37.5)
31 - 35	5	10 (31.25)	7 (29.1)
36 - 40	4	1 (3.125)	3 (12.5)
Settlement			
Urban	22	14 (43.75)	9 (37.5)
Rural	10	18 (56.25)	15 (62.5)
Clinical types			
Acute	-	23 (71.8)	18 (75)
Subacute	-	2 (6.25)	1 (4.1)
Chronic	-	3 (9.3)	2 (8.3)
Relapsed	-	4 (12.5)	3 (12.5)
Number of symptoms			
0 - 3	16	1 (3.1)	-
3 - 5	7	18 (56.25)	6 (25)
> 5	1	13 (40.6)	18 (75)
Number of pregnancies prior to the study			
0	3	2 (6.25)	1 (4.1)
1	9	2 (6.25)	1 (4.1)
2	15	8 (25)	6 (25)
≥3	5	20 (62.5)	14 (58.3)
Number of spontaneous abortions prior to the study			
0	32	32 (100)	24 (100)
1	-	-	-
2	-	-	-
Trimester of pregnancy			
1	12	3 (9.37)	4 (16.6)
2	12	14 (43.75)	11 (45.8)
3	8	15 (46.8)	9 (37.5)
Pregnancy outcomes			
Term delivery	29	16 (50)	4 (16.6)
Preterm Delivery	1	6 (18.75)	9 (37.5)
Low birth weight	2	9 (28.1)	8 (33.3)
Spontaneous abortion in 1 st trimester	-	1	1 (4.1)
Spontaneous abortion in 1 st trimester	-	-	2 (8.3)

RESULTS

In the control group, the mean age was 27.9 years. Out of 32 healthy pregnant women 29 delivered at term, two neonates had low birth weight and one ended in preterm delivery. The neonates were all healthy. There were no congenital defects or any other anomaly.

In group B, the mean age was 28.9 years. Out of 32 women in this group; 23 were acute BCS, two were sub-acute, three chronic and four women had relapsed. The outcome of pregnancies in women with BCS was as follows: 16 (50%) term deliveries, nine (28.1%) low birth weight, six (18.75%) preterm delivery and one abortion in the first trimester. The abortion was observed in a pregnant woman who had chronic BCS. There was no maternal mortality (Table 1).

In the B + AVH group the mean age was 29.5 years. Out of 24 women in this group: 18 (75%) were acute BCS one (4.1%) sub-acute, two (8.3%) chronic and three (12.5%) women had relapsed. Twelve out of the 24 (50%) pregnant women were positive for hepatitis B, seven (29.1%) for hepatitis C and five (20.8%) for acute hepatitis A. The outcome of pregnancy was as follows: nine (37.5%) preterm delivery, eight (33.3%) low birth

weight, four (16.6%) term deliveries and three (12.5%) abortions; one abortion was in the first trimester and had hepatitis B, two were in the second trimester. One had hepatitis B and the other had hepatitis C. There was no maternal mortality.

Preterm delivery occurred in 18.75% of group B women and 37.5% group B + AVH. Compared to control group, occurrence of preterm delivery in group B was statistically significant ($\chi^2 = 19.36$, $p = 0.004$). The B + AVH group had an increased risk for preterm delivery than B group ($\chi^2 = 4.83$, $p = 0.028$). Low birth weight risk was also increased in B and B + AVH groups ($p < 0.0001$). Antepartum hemorrhage was a frequent complication in B + AVH group compared to the B and control group ($\chi^2 = 13.928$; $p < 0.001$).

Out of the 32 pregnant women with BCS 62.5% had more than three children, whereas 58.3% of the 24 pregnant women in B+AVH group had more than three children. We also noted that the number of previous pregnancies had no effect on the risk of low birth weight ($\chi^2 = 0.182$; $p < 0.913$) and preterm delivery ($\chi^2 = 6.507$; $p < 0.164$). Also, we did not find any relation between course of the diseases and

the trimester ($\chi^2 = 6,218$; $p < 0,183$). Runny cheese was found to be the most common causative agent contaminated with BCS ($\chi^2 = 43,402$; $p < 0, 0001$) as the cheese is made from unpasteurized milk ($\chi^2 = 37.877$; $p < 0, 0001$) in the region.

The physiological changes and mean values of biochemical data of healthy pregnant women and pregnant women with BCS and AVH are shown in Table 2. Out of 32 cases in group B, 40.6% had less than five symptoms whereas 24 cases (75%) had more than five symptoms. The number of symptoms were more frequent in B + AVH group ($\chi^2 = 64.65$; $p < 0, 0001$). The most frequently seen symptoms in group B were arthralgia in 26 (81.2%), sweating in 23 (71.8%) and myalgia in 24 (75%), while nausea in 22 (91.6%), pruritis in 18 (75%), loss of appetite in 19 (79.1%) and arthralgia in 17 (70.8%) women in the B + AVH group. The most frequent clinical findings were fever in 22 (68.75%), hepatomegaly in nine (28.1%) and splenomegaly in seven (21.8%) in B group and jaundice in 22 (91.6%), hepatomegaly in 15 (62.5%) and splenomegaly in 14 (58.3%) in B + AVH group. The most frequent laboratory finding was high C-reactive protein level in 22 (68.7%) and high ESR in 28 (87.5%) in B group, elevated liver enzymes 24(100%) in B+AVH group. Three pregnant women in B+AVH group had maculopapular-urticarial rash and two of them had petechiae–purpura followed by hemorrhage. All pregnant women who had BCS received antibrucellosis therapy. Six pregnant women in B+AVH group and one in B group interrupted the therapy for a while and after normalization of the liver enzymes the treatment was restarted. Five pregnant women in the B group (one acute, one subacute, three chronic) relapsed after co-trimoxazole treatment. In B + AVH group none of the patients received antiviral therapy except supportive and antibrucellosis therapy.

DISCUSSION

This study aims to answer some key questions regarding BCS and AVH during pregnancy, in order to provide healthcare professionals with updated information on the current knowledge in this field. In southeast Turkey, the seroprevalence of BCS and AVH is the highest in the country. Therefore, we had an opportunity to compare these two diseases in every aspect in a special cohort of pregnant women.

To the best of our knowledge, this study is the first and also the only study that investigates the implications of BCS and AVH co-infection during pregnancy.

In humans, there is uncertainty regarding effects of brucella in pregnancy^[1]. Our study demonstrates that BCS and AVH do not have a major deleterious effect on pregnancy. We have not observed any mortality.

Table 2. The presenting physiological changes and mean values of biochemical data of pregnant women with Brucellosis and AVH

Test	Healthy	B Group	B + AVH Group
Age (years) (mean)	27.9	28.9	29.5
High fever(> 38 °C)	0	22	11
Arthralgia	3	26	17
Pruritis	1	7	18
Sweating	9	23	19
Headache	2	12	15
Hepatomegaly	0	9	15
Splenomegaly	0	7	14
Total bilirubin	1	1.8	7.6
AST (IU/ml) (mean)	20	42	208
ALT (IU/ml) (mean)	24	76	380

e aminotransferases (IU/ml); Alanine aminotransferases (IU/ml)

Divergent opinions exist over the maternal and fetal outcome of the pregnancies associated with BCS and AVH^[1,9,10-12]. As an example; Nassaji *et al* observed that intrauterine death and spontaneous abortion risk is not elevated in pregnant women with BCS^[10]. However, some studies reported that there is high risk for intrauterine fetal death and spontaneous abortion in BCS in pregnancy^[9,11,12]. In our study, we have observed only one abortion out of 32 pregnant women with BCS. Therefore, we cannot link the spontaneous abortion to BCS in pregnancy. Also, there are some reports which show that BCS alone in pregnancy has no effect on the incidence of congenital malformations, stillbirths and abortions^[13-15]. In our study, we have observed three (14.2%) spontaneous abortion in B + AVH group. In conclusion, our results show that BCS increases spontaneous abortion risk in pregnant women who have AVH ($p < 0.001$). One other striking finding in our study was that there were no birth defects or stillbirths in pregnant women who had BCS alone or who were also infected with AVH.

According to our study; we observed that antepartum hemorrhage was more frequent in pregnant women who were infected with BCS and AVH compared with pregnant women with BCS alone ($p < 0.001$). Some studies also show the relationship between BCS and antepartum hemorrhage during pregnancy^[16-18].

We have observed increased risk for preterm delivery in B and B + AVH group. Most studies also support the link between preterm delivery and BCS in pregnancy^[1,9,11,12]. Opinions differ over the maternal and fetal outcome of pregnancy associated with viral hepatitis. Current studies and case reports have shown an increased risk of developing preterm delivery in pregnant women with BCS and acute liver disease^[17,19-21]. Hieber *et al*^[14] also reported that BCS increases the incidence of prematurity (type B 31.6%; nontype B 25%; overall 27.6%) over that seen in the general delivery population (10 to 11%).

BCS and AVH do not appear to be teratogenic. However, there appears to be a higher incidence of low birth weight among infants born to mothers with BCS infection during pregnancy^[22-24]. We have found an increased risk for low birth weight during pregnancy in B and B + AVH groups ($p < 0.0001$). Therefore, we conclude that low birth weight can be seen as a pregnancy outcome in BCS and concurrently occurring AVH.

We have also noted that previous number of pregnancies did not affect the incidence of low birth weight and preterm delivery. We could not find many studies on these issues. The ones that we found were compatible with our findings. Nassaji *et al* reported that they have not found any significant relationship between number of previous pregnancies and complication rates^[10]. Khan *et al* reported that there were more risks in the first and second trimester than the third trimester^[12].

We observed that in the B + AVH group the number of symptoms were more than in the B and control group. The symptoms were more severe in B + AVH group. This also increased the risk of complications.

In all studies, authors mention that BCS occurs after consumption of raw milk. Runny cheese made from unpasteurized milk and consumed in this region was contaminated with *Brucella*. This might be due to ignorance. The local population has learned not to consume raw milk and its products but still they have not recognized that runny cheese is nowadays the main source of *Brucella*.

CONCLUSION

Brucellosis and AVH in pregnancy are well-tolerated diseases even if they occur at the same time. Treatment of BCS with appropriate antibiotics is possible even in the presence of liver dysfunction. Antiviral therapy is not needed. BCS alone or with AVH in pregnant women are risk factors for preterm delivery and low birth weight.

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Original Article

Pattern of Chromosomal Abnormalities in Pediatric Acute Lymphoblastic Leukemia (ALL)

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ABSTRACT

Objective: To study the cytogenetic profile of newly diagnosed patients with pediatric acute lymphoblastic leukemia (ALL)

Design: Prospective case control study

Setting: Tertiary care hospital in India

Subjects: Newly diagnosed patients with pediatric ALL

Interventions: Karyotype analysis of bone marrow aspirate samples by routine G-Banding technique and analysis as per International System for Cytogenetic Nomenclature (ISCN), 2005 criteria.

Main Outcome Measures: Cytogenetic parameters

Results: The study included 23 male and eight female patients (M:F = 2.8:1). ALL-L2 was the most common morphological phenotype (18 / 31, 58%). Sixteen out of thirty one (51.6%) patients were hypodiploid ($2n < 46$), 10 / 31(32.0%)

hyperdiploid ($2n > 46$) and 5 / 31(16.0%) aneuploid. Among hypodiploid groups, nine (29.0%) had modal chromosome number as 40-45, five (16.0%) as 31-39 and two (6.5%) as 25-30. Among hyperdiploid group, 7 (22.5%) had modal chromosome number as 51-60 followed by $2n = 47-50$ (three patients, 6.5%). The chromosomes (Chr) 2, 10, 12,15,17,19 were commonly deleted in hypodiploid cell lines whereas gain of Chr 4, 8, 10,14 and 20 were observed in hyperdiploid group. Translocation t (10;14), t (9;22), t (2;22), t (8;22) and t (4;11) were seen in 04 (12.8%), 03 (9.6%), 02 (6.4%each) and one patient (3.2%) respectively.

Conclusion: Adverse cytogenetic parameters such as hypodiploidy and translocations such as t (10;14), t (9;22), t (2;22), t (8;22) and t (4;11) were more common in our cohort of patients.

KEY WORDS: chromosomes, cytogenetics, G-Banding, ploidy, translocations

INTRODUCTION

Molecular genetic analysis of acute leukemia has been at the forefront of research in the pathogenesis of cancer because the presence of recurring chromosomal abnormalities provides immediate clues to the genetic events leading to leukemia and the means to clone and identify the dysregulated oncogenes. In the majority of acute leukemia and 54 to 78% of adult acute myeloid leukemia (AML), cytogenetic abnormalities are detected on karyotype analysis of peripheral blood or bone marrow. Large clinical studies of both acute myeloid and lymphoblastic leukemia (ALL) have demonstrated that pretreatment diagnostic cytogenetics is one of the most valuable prognostic indicators for acute leukemia^[1]. Recognized risk groups defined by age, sex, presenting total leukocyte count (TLC), organomegaly, mediastinal adenopathy have been shown to contain subgroups of patients with different outcome predicted by karyotype, early response to therapy, immunophenotype, and molecular genetic abnormality. Hyperdiploid patients

with modal chromosomal numbers greater than 50 fare best, whereas pseudodiploidy and hypodiploidy are associated with generally poor response. Patients with any translocation have a six fold greater risk of early treatment failure than those without such abnormalities^[2].

The aim of the present article was to study the clinicopathological features and various chromosomal abnormalities in pediatric ALL with a brief review of literature.

SUBJECTS AND METHODS

This was a prospective study done over a period of one year (December 2008 to November 2009). The Institutional Ethics Committee had approved the study and written consent was obtained from the parents of the patients. Forty-four (44) patients (30 male, 14 female, M:F = 2:1) of newly diagnosed pediatric (1 to 14 years) ALL were included for cytogenetic analysis. Infants, those in induction and maintenance chemotherapy and relapse were excluded from the study. The

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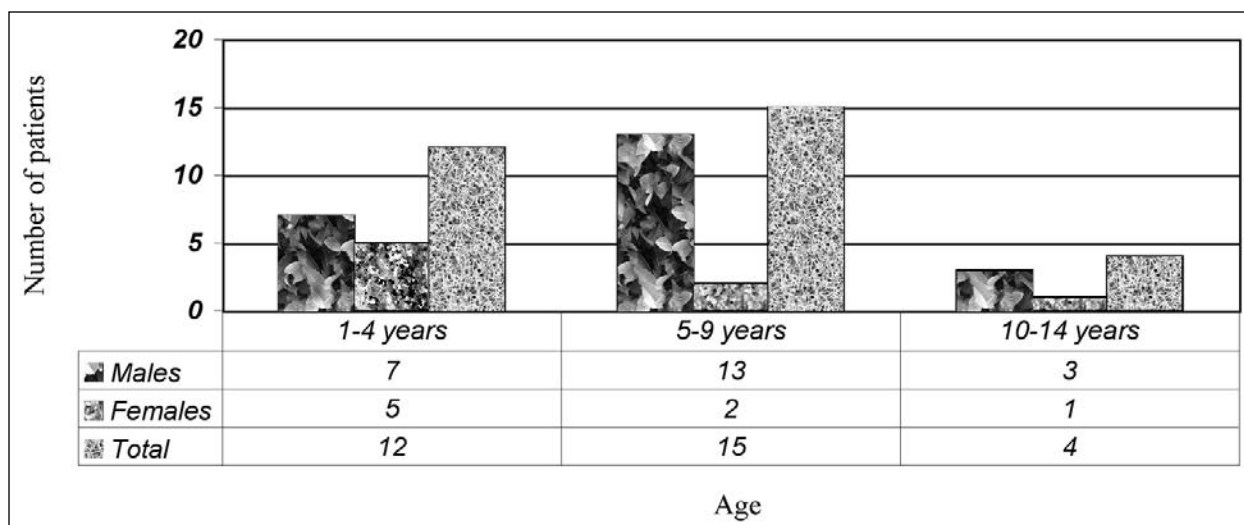


Fig. 1: Age and sex distribution in 31 cases of acute lymphoblastic leukemia (ALL)

French-American-British (FAB) criteria^[3] were used to categorize ALL from Leishmann stained bone marrow aspirate smears. Patients' clinical details such as age at presentation, gender, general physical condition and duration of symptoms, history of fever, bleeding manifestations, bony tenderness, joint abnormalities, organomegaly, lymphadenopathy, and radiological findings (chest and bone X-ray) were obtained from patient files. Routine hematological parameters (at the time of first admission) such as hemoglobin (Hb; grams per liter), total leukocyte count (TLC; $\times 10^9$ /liter), total platelet count (TPC; $\times 10^9$ /liter) were obtained from Beckman Coulter counter LH500.

Bone marrow aspirate samples were subjected to routine cytogenetic analysis (G-banding) by following Direct Flame Drying Giemsa staining technique^[4]. Well-spread metaphase plates were obtained in 31/44 cases for analysis. A minimum of 15 to 20 well-spread metaphase plates were analyzed in all cases and the modal number of chromosome (defined as the highest number of chromosome present among 15-20 metaphase plates studied for individual patient and hence the indicator of ploidy) was calculated for each patient. The karyotype analysis was performed as per International System for Cytogenetic Nomenclature (ISCN) 2005 criteria^[5]. The results of cytogenetic analysis were correlated with patients' clinical and hematological parameters for risk stratification.

RESULTS

The clinical and laboratory parameters in all the 31 patients of ALL are presented in Table 1. As depicted in Fig. 1, 15 / 31 (48%) patients were in the age group of 5 - 9 years with male predominance. Eighteen of 31 patients (58%) belonged to ALL-L2 category. Seventeen out of 31 (54.5%) patients revealed abnormal and normal metaphase plates, 10 / 31(32%) showed only abnormal plates whereas normal / near normal

metaphase plates were seen in only four patients (13%, Table 2). A high proportion of patients (16 / 31, 51.6%) had hypodiploid karyotype (modal number of chromosomes less than 46), whereas hyperdiploidy

Table 1: Age, gender, clinical presentation, and routine hematological parameters in pediatric acute lymphoblastic leukemia (ALL) (n = 31)

Parameters	No. of patients	% of total
Age (year)		
1 - 9	27	87
10 - 14	4	13
Male / Female	23 / 8	74 / 26
Symptoms		
Malaise and fatigue	31	100
Fever	24	77.4
Bleeding manifestation*	18*	58
Joint pain, bone pain, limping†	4†	13
Clinical signs		
Pallor	20	64.5
Cervical +/- axillary lymph node	19	61.2
Purpura	12	38.8
Palpable liver +/- spleen	12	38.8
Bony/sternal tenderness	5	16
Mediastinal mass	3	9.6
Hemoglobin (< / > 80 g/l)	13 / 18	42 / 58
TLC [‡] ($\times 10^9$ /l)		
< 10	6	19.4
10 - 50	15	48.4
> 50	10	32.2
TPC [§] ($\times 10^9$ /l)		
<100	24	77.5
>100	7	22.5
Bone marrow		
Blast (< / > 50 %)	17 / 14	54.8/45.2
FAB ^ε -L1	12	38.8
FAB-L2	18	58
FAB-L3	1	3.2

* includes 12 patients with purpura, 4 with nose bleed, and rest 2 with melena, † patients with initial presentation of joint and or bone involvement, misdiagnosed as juvenile rheumatoid arthritis, ‡ total leukocyte count, § total platelet count, ε FAB; French-American-British

Table 2: Type of metaphase plates obtained in 31 cases of ALL

Type of metaphase plates	No. of cases	%
Abnormal & normal	17	54.8
Abnormal only	10	32.0
Normal / near normal	04	13.0

($2n > 46$), aneuploidy were seen in 10 (32.0%), and five (16.0%) patients respectively (Table 3). Hypodiploid blasts with modal chromosome number between 40 and 45 were observed in 9 / 16 patients whereas those with 31 to 39 were seen in five patients, and near haplodiploidy in only two (Fig. 2). The Chr 2, 10, 12, 15, 17, 19 were commonly deleted in hypodiploid cell lines whereas gain of Chr 4, 8, 10, 14 and 20 was observed in hyperdiploid group. (Table 4, Fig. 3).

A majority of patients (18 / 31, 58%) had no detectable structural abnormalities on conventional G-banding technique whereas thirteen (41.9%) showed chromosomal translocations. Translocation t (10; 14) was the commonest structural abnormality seen in four (12.8%) followed by t (9; 22) (Fig. 4 & 5), t (8; 22), t (2; 22) and t (4; 11) in three, two, two and one patient respectively. Stickiness (Fig. 6), fragmentation, and endomitosis (Fig. 7), as secondary chromosomal aberrations, were observed in significant proportion of our patients (Table 5).

DISCUSSION

ALL is the most common cancer diagnosed in children and represents 23% of cancer diagnoses among children younger than 15 years with a sharp peak among children aged 2 to 3 years^[6]. The majority of patients in our series were male in the age group of 5 - 9 years with ALL-L2 predominant phenotype.

Generalized malaise and fatigue was the most common presentation (100%) followed, in frequency, by fever with or without infection (77.4%), and bleeding manifestation (58%, mostly purpura). Four patients (13%) presented with predominant skeletal

Table 3: Distribution of FAB* morphology according to numerical abnormalities in ALL[†]

Numerical changes	L1‡	L2§	L3ε	Total cases	%
Hypodiploid ($2n < 46$)	07	09	00	16	51.6
Hyperdiploid ($2n > 46$)	05	05	-	10	32.0
Aneuploid		04	01	05	16.0

* French American British, † acute lymphoblastic leukemia, ‡ ALL-L1, § ALL-L2, ε ALL-L3

symptoms such as joint pain, swelling, and difficulty in walking which led to the misdiagnosis of juvenile rheumatoid arthritis, as has been described in the literature (Table 1)^[7].

Clonal chromosomal abnormalities are found in upto 80% of patients with ALL. These are closely related to the biology of the disease and indicate the genes involved in leukemogenesis. Cytogenetic classification is based on the number of the chromosomes (ploidy), structural alterations (translocation), and immunophenotype which are important in both childhood and adult ALL to distinguish low from high risk patients^[8-12].

The incidence of cytogenetic abnormalities detected by routine karyotype analysis have led to the following distribution in pediatric ALL; pseudodiploid (25 - 40%), normal karyotype (20 - 30%), hyperdiploid (10 - 25%), and hypodiploid (4 - 10%)^[2,13,14]. Similar to our observation (51.6% hypodiploid Vs 32% hyperdiploid), various Indian studies have found opposite results, *i.e.*, the chromosomal abnormalities associated with poorer prognosis have been observed more frequently from India than those associated with good prognosis. There has been a marked increased in prevalence of hypodiploid karyotype (30 - 40%) than hyperdiploidy (15%) among Indian ALL patients^[15, 16]. Similarly, a higher percentage of adult ALL patients were found to be hypodiploid in another study from neighboring Pakistan^[17].

Table 4: Age, FAB*subtypes and numerical changes in all cases of ALL[†]

Type of numerical changes	No of patients	%	Age range (yrs)	ALL-L1	ALL-L2	ALL-L3	Chromosome gain (+) / loss(-)
Hypodiploid ($2n = 25 - 30$)	02	6.4	4 - 5	-	02	-	-6, -9, -13, -15, -17, -18, -20
Hypodiploid ($2n = 31 - 39$)	05	16.0	1 - 14	03	02	-	-2, -10, -15, -17, -19, -20
Hypodiploid ($2n = 40 - 45$)	09	29.0	1 - 10	02	07	-	-3, -10, -11, -18, -20
Hyperdiploid ($2n = 47 - 50$)	03	9.6	2 - 5	02	01	-	+14, +17
Hyperdiploid ($2n = 51 - 60$)	07	22.5	3 - 8	04	03	-	+4, +8, +10, +14, +20
Aneuploid	05	16.0	2 - 10	03	01	01	-9, -10, -14, -17, +12, +19

* French American British, † acute lymphoblastic leukemia

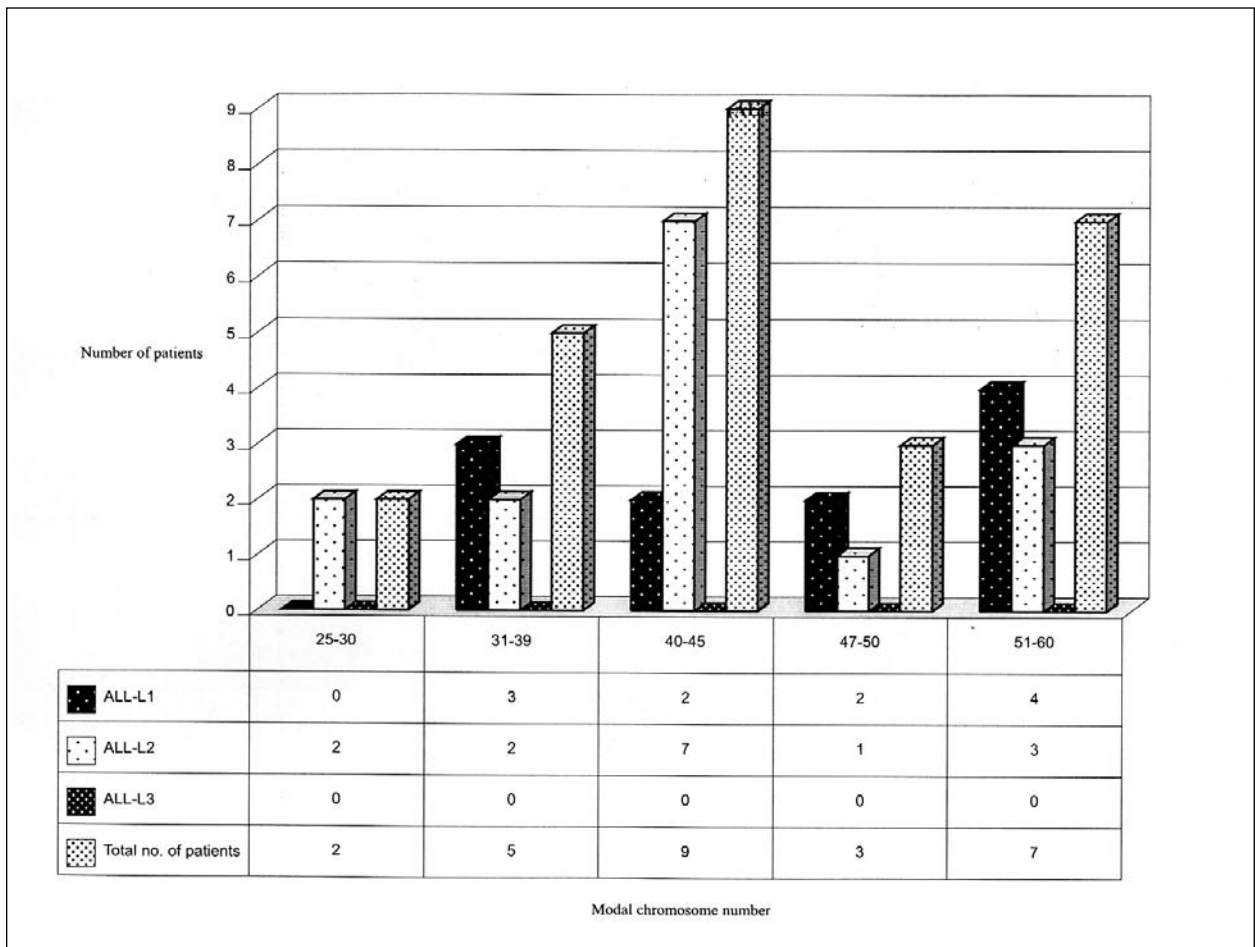


Fig. 2: Blast morphology and numerical chromosomal abnormality in acute lymphoblastic leukemia (ALL).

High hyperdiploid ALL is one of the most common malignancies in children. It is characterized by gain of chromosomes, typically +X, +4, +6, +10, +14, +17, +18, and +21^[18-21]. High hyperdiploidy (2n = 51 to 65) generally occurs in cases with clinically favorable prognostic factors (patients aged 1 - 9 years with a low WBC count) and is itself an independent favorable prognostic factor. Trisomy of Chr 4, 8, 10, 14 and 20 was noted among hyperdiploid group in our study. In spite of adverse clinical and laboratory parameters in these patients (Table 1), good cytogenetic parameters were predictive of a favorable outcome following chemotherapy as has been described in the literature^[21-23].

Compared to hyperdiploid group, progressively worse outcome is associated with a decreasing chromosome number (hypodiploidy). Cases with 24 to 28 chromosomes (near haploidy) have the worst outcome and those with fewer than 44 chromosomes have a worse outcome than patients with 44 or 45 chromosomes in their leukemic cells^[2, 24, 25]. In the present study, hypodiploid cell lines of 40 - 45 were more common which were characterized by deletion

of Chr 2, 10, 12, 15, 17, 19 (Fig. 3). Demonstration of near haploidy in two of our patients (age 3 & 4 years) was an example of 'age restricted leukemia'^[26] and worst prognosis as both the patients died during their initial investigation work-up.

Chromosomal abnormalities that cannot be resolved by G-banding may be detected by molecular

Table 5: Structural abnormalities in all cases of ALL[†]

Structural abnormalities	No. of cases	%
A. No identifiable abnormalities	18	57.6
B. With structural abnormalities		
I Primary chromosomal translocation	13	41.6
1. t(† (10; 14)	04	12.8
2. t (9; 22)	03	9.6
3. t (4; 11)	01	3.2
4. t (2; 22)	02	6.4
5. t (8; 22)	02	6.4
II Secondary/additional aberration		
1. Stickiness	21	67.0
2. Chromatid fragmentation	19	60.8
3. Pulverization	17	54.5

† acute lymphoblastic leukemia, ‡ translocation

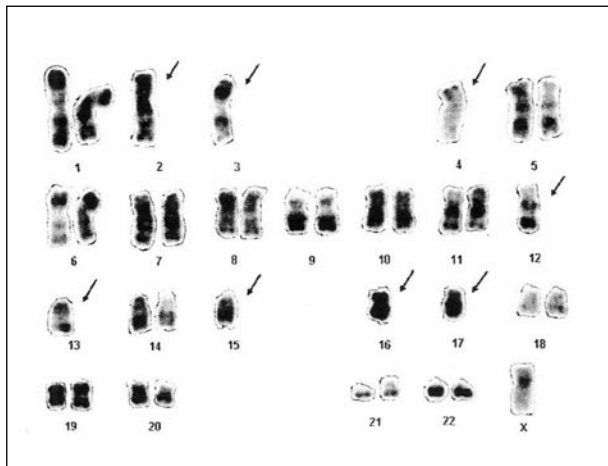


Fig. 3: G-Banded male karyotype in ALL patient showing multiple whole chromosomal deletions such as deletion of Chr 2, 3, 4, 12, 13, 15, 16, 17&Y (arrow). This is an example of numerical chromosomal abnormality in ALL [37, X, hypodiploidy and aneuploidy] (G-T-G Banding, 40X).

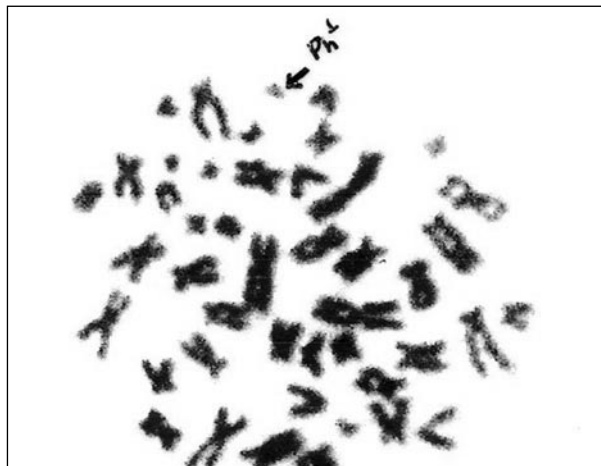


Fig. 4: Metaphase spread of chromosomes in a male child with ALL showing altered chromosome 22 following translocation [Philadelphia chromosome (Ph1) (arrow)] (46, XY). Detailed structural abnormalities of chromosome 9 is not appreciated at this resolution (Giemsa stain, 40X). Due to low resolution GTG banding technique, Ph1 chromosome may be missed in up to 2-3% cases.

cytogenetic techniques such as fluorescence in-situ hybridization (FISH). The FISH technique have become an integral part of cytogenetic analysis and must be regarded as complementary, not replacement tools^[27, 28].

The t (12; 21) (p13, q22) is the most common structural abnormality among pediatric B - ALL and carries a favorable prognosis. However, this can be missed by routine low resolution G-banding technique and hence remain cryptic^[8]. In a recent study, by using conventional cytogenetics and FISH technique^[28], t (12; 21) (q13; q 22) was found to be the most common (22%), followed in frequency, by 9p abnormalities (10%), t (1;19) (8%), t (9; 22) (8%), and 11q23 abnormality (5%). Rare translocations such as t (5;12), t (14,19), t (12;16),

der (1) t (1,12), and t(5,15) were the rare structural abnormality noted. Comparable to our observations, translocation t (9; 22) was the most common structural abnormality detected in other studies from Taiwan and India^[14, 29, 30].

Barring the age factor, clinical parameters such as male gender, organomegaly, high TLC, thrombocytopenia, and ALL-L2 phenotype were more common in our patients at the time of first admission. These findings were in accordance with poor cytogenetic parameters such as hypodiploidy and translocations [t (10; 14), t (9; 22), etc] and thus, predictive of adverse outcome in our study.

The mechanism of various numerical abnormalities in leukemia is complex and least understood^[31].

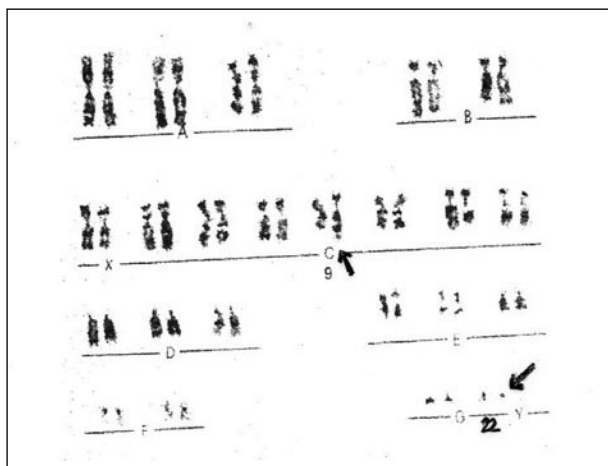


Fig. 5: G-Banded karyotype in a female child of ALL showing primary structural abnormality in the form of translocation between long arms of chromosome 9 and 22 [t (9; 22)] (arrow). The chromosome 22 after the rearrangement is known as the Philadelphia chromosome (46, XX, G-T-G Banding).

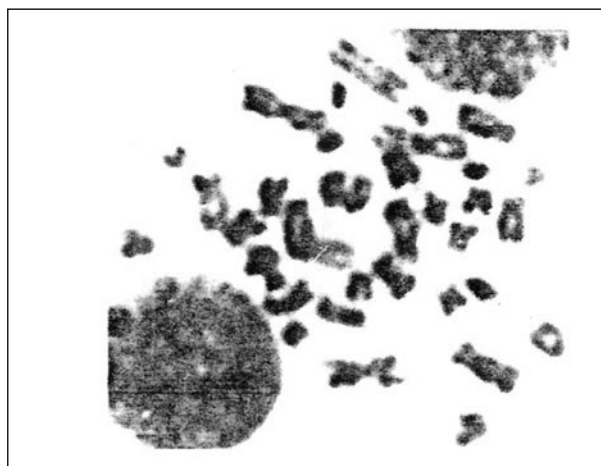


Fig. 6: Secondary chromosomal abnormalities in ALL blasts characterized by stickiness between the chromosomes leading to poor quality of chromosome separation by hypotonic saline treatment during routine G-banding technique (Giemsa, 40X)

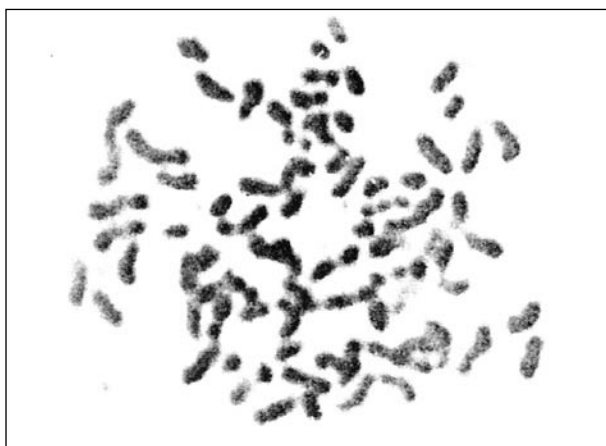


Fig. 7: Secondary chromosomal abnormality in ALL characterized by endomitosis which refers to the doubling of chromosomes in the cell nuclei without mitosis leading to polyploidy. (Giemsa, 40X)

Various theories such as 'non-disjunction at mitosis', 'formation of micronuclei', 'chromosome lagging', 'deletion of parts of chromosomes', or 'telomeric loss' have been postulated to explain the occurrence of hypodiploidy, hyperdiploidy, and aneuploidy.

Secondary chromosomal abnormalities in leukemia are not uncommon^[32]. The exact mechanism leading to these abnormalities in the leukemic cells is still not known. These aberrations are mostly unstable ones causing loss of genetic material and their frequency seems to increase with the progression of the disease. Both numerical and structural abnormalities are the result of accumulated genetic errors during repeated mitotic perpetuation of leukemic cells or the effects of the products of the transformed cells.

Cytogenetic studies in ALL are particularly difficult owing to the frequent low mitotic index of the abnormal blasts and the notoriously poor chromosome morphology (stickiness, poor separation following hypotonic saline treatment) (Fig. 6)^[27], which possibly explained the relatively low number of patients studied in our series (31 / 44).

Although the current trend is to use more sophisticated methods such as spectral karyotyping and multicolored-FISH analysis and flow cytometry *etc*, various practical issues such as availability, cost factor, and lack of expertise are still the major reasons rendering these tests to be confined to the specialized centers only. On the other hand, the routine G-banding technique, though time consuming, is cost effective, requires minimal expertise, and hence can be used as routine screening tool in most of the diagnostic work-up for various chromosomal anomalies. In addition, non-performance of the test at the time of first remission and / or relapse was attributed to the poor follow-up system at our Institute as most of the patients, after their diagnosis, were either referred to specialized oncology centers or left the hospital against medical advice.

CONCLUSION

Adverse clinical, laboratory, and cytogenetic parameters were observed in a high percentage of ALL patients in our study compared to the world literature. Therefore, mandatory cytogenetic studies should be a part of diagnostic evaluation of each patient of acute leukemia in order to validate our present findings and for proper patient care.

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Original Article

The Diagnostic Value of Sinus-Track Cultures in Secondary Pediatric Chronic Osteomyelitis

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ABSTRACT

Objective: To determine and compare the diagnostic value and accuracy of culture of material from a sinus track with culture of material from bone specimens

Design: Retrospective study

Setting: Dicle University Medical School and Batman State Hospital, Turkey

Subjects: Twenty-one patients with secondary chronic osteomyelitis (COM). Material for culture was taken from the sinus as well as the bone specimens

Interventions: Surgery for COM

Main outcome measures: The diagnostic value of sinus track culture

Results: The mean age of patients was 8.5 ± 3.8 years. 15 (71.4%) were male and six (28.6%) were female. Organisms

isolated from bone cultures were *Staphylococcus* 71.4% (15 / 21), *Pseudomonas aeruginosa* 9.5% (2 / 21), *Escherichia coli* 9.5% (2 / 21), *Proteus mirabilis* 4.8% (1 / 21), *Klebsiella pneumoniae* 4.8% (1 / 21), respectively. Cultures of sinus track material and bone specimens gave identical results in 47.6% of patients.

Conclusion: This study shows that if treatment of COM was planned according to the microbiological analysis of material from the sinus-track, it may not result in recovery every time. We found approximately 48% concordance between sinus-track and bone cultures. In other words, antimicrobial therapy guided by antibiograms of bacteria isolated from sinus-track would be inappropriate in 52% of patients with COM and result in treatment failure.

KEY WORDS: bacteriology, childhood, chronic osteomyelitis, sinus-track

INTRODUCTION

Osteomyelitis is an inflammatory process accompanied by bone destruction and caused by an infecting microorganism. The infection can be limited to a single portion of the bone or can involve several regions, such as marrow, cortex, periosteum, and the surrounding soft tissue^[1]. It can be caused by bacteria, fungi and a variety of other organisms. Among the pathogenic microorganisms *Staphylococcus aureus* is by far the most commonly involved in all age groups, including newborns. Group A Streptococcus is next in frequency but constitutes fewer than 10% of all cases^[2].

Osteomyelitis in pediatric patients occurs uniquely because of the blood supply, which may be compromised by trauma^[3]. Chronic osteomyelitis (COM) can be primary, when it arises from failed treatment of acute hematogenous osteomyelitis (AHO) or secondary, when it is caused by trauma to the bone, open fractures or from postoperative infection^[4]. The hallmark of

COM is bone necrosis and, as opposed to AHO in which medical treatment results in > 90% cures, COM often requires multiple surgical procedures and long term antibiotics^[5].

The most important step in COM is to isolate the offending organisms so that the appropriate antimicrobial therapy can be chosen^[6]. In cases of COM, sinus-tracks frequently develop from infected bone to the skin. Several investigators have used cultures of specimens from sinus-tracks to identify the pathogens^[7, 8]. In doing so, they have assumed that bacterial cultures from the sinus-track originate from bone infection itself. Material taken from an open sinus-track by swabbing will give misleading results because the isolates may include non-pathogenic microorganisms that are colonizing the site. The aim of this study was to retrospectively compare the diagnostic value of the sinus-track and bone specimen cultures in secondary pediatric COM.

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SUBJECTS AND METHODS

The medical records of 21 consecutive patients with COM who were treated and followed up at the Departments of Orthopedics and Traumatology and Infectious Diseases, Dicle University Hospital and Batman State Hospital, Turkey, between May 2005 and April 2007, were reviewed. Out of 21 patients, the medical records of 17 patients were published in our other study that included heterogeneous patient groups^[9].

In this study, COM was defined as a bone infection that was worse or had not improved clinically or microbiologically after ≥ 10 days of evolution, independent of the presence or absence of surgical and / or antimicrobial therapy. Patients were considered to have COM, if they had one or more sinus-tracks associated with their bone infection plus at least one of the following: (i) positive bone culture, (ii) surgical or histopathologic confirmation of bone infection or (iii) radiographic evidence of bone infection. Conventional X-ray findings were used for diagnosis principally. When it was inadequate, other imaging techniques such as scintigraphy and magnetic resonance imaging were used. Nevertheless, sequential specimens taken from the sinus-tracks and bones were not used, and only two bone specimens were acceptable: bone biopsy and bone marrow biopsy. Furthermore, patients with orthopedic device were also not included in the study.

If antibiotics were being administered, they were discontinued at least 48 hours before material was obtained for incubation and histological examination. The histological findings of COM were defined as exhibited areas of woven bone and fibrosis with large numbers of lymphocytes, histiocytes, and plasma cells in the absence of neutrophils^[10]. In cases meeting these criteria; we noted age, sex, laboratory results such as white blood cell count (WBCc), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), involved bone, time with COM, mechanism of bone infection, type of specimen cultured and microbiologic identification and susceptibility pattern of organisms grown in aerobic and anaerobic atmosphere.

In the operating room, before the incision was made, specimens were obtained from the sinus-track for aerobic and anaerobic culture. Specimens of bone obtained from curettage, and of bone from the bed of involved bone were obtained during the operation for similar cultures. The bone specimen were placed into a sterile container with non-bacteriostatic saline and walked to microbiology laboratory by an operating room nurse within 30 minutes. However, the sinus-track specimens were inoculated on plates immediately, by the bedside, without using transport media.

The material was routinely streaked into eosin-methylene blue agar and 5% sheep blood agar. The two plates were incubated in air at 37 °C for 24 hours, for aerobic microorganisms. For the isolation of anaerobes, specimens were plated onto prereduced vitamin K1 enriched Brucella blood agar, anaerobic blood agar plates containing kanamycin and vancomycin, and anaerobic blood plates containing colistin and nalidixic acid, and then samples were inoculated into enriched thioglycolate broth. The plated media were incubated in a Zip-Loc plastic bag to maintain the increased CO₂ atmosphere at 37 °C and examined at 48, 96, and 120 hours. The thioglycolate broth was incubated for 14 days. Smears from colonies that grew under either aerobic or anaerobic conditions were stained with Gram-stain; Gram-positive organisms were identified by conventional techniques, Gram-negative organisms were identified using Sceptor Systems (Becton-Dickinson, Maryland, USA). Its susceptibility was evaluated using disc diffusion testing performed as recommended by the National Committee for Clinical Laboratory Standards (NCCLS)^[11]. If cultured microorganisms were not present and the clinical features were compatible, samples were cultured for mycobacterium and fungus.

Isolates from the infected bone were compared with isolates from sinus-track for each patient. Sinus-track specimens were considered concordant with the bone when they grew exactly the same pathogens isolated from the bone and had identical susceptibility patterns. Concordance was calculated for all causes and for COM caused by *S. aureus*, the agent most commonly isolated from infected bone. Single and multiple microorganisms were isolated from tibia in 10 and four patients, respectively. On the other hand, multiple microorganisms were not isolated from other sites in any patients.

Descriptive and frequency statistical analyses were performed by using the Statistical Package for the Social Science (SPSS) for Windows, version 13.0 software (SPSS, Chicago, IL, USA).

RESULTS

In this study, 21 patients with COM were analyzed. During this study period, 26 patients were diagnosed as having COM, and five patients were excluded because antibiotic treatment was not stopped 48 hours before bone culture ($n = 3$), and lack of bone ($n = 2$). 21 patients met the inclusion criteria; their demographic data are detailed in Table 1. Out of 21 patients, 15 (71.4%) were male and six (28.6%) were female with a male to female ratio of approximately 2.5:1. The mean age of the patients was 8.5 ± 3.8 years (range, 2 - 15 years).

The source of COM was known in all patients and they all had secondary COM. Previous open fracture

(n = 13), previous closed fracture managed non-operatively (n = 5), previous blunt trauma to limb without fracture (n = 2) and previous bone surgery (n = 1) were the reasons of secondary COM. Tibia (n = 14, 66.6%) and femur (n = 3, 14.3%) were the most frequent foci of the COM, followed by fibula associated with the tibia (n = 2, 9.5%), vertebra (n = 1, 4.8%), humerus (n = 1, 4.8%). The onset of symptoms of COM occurred from 35 - 225 days (mean, 68.6 ± 21.9) before admission.

Laboratory findings of patients such as ESR, CRP and WBC count were measured in all patients at admission. ESR ranged 28 - 125 mm / h (mean, 72.1 ± 27.9 mm / h). All patients had ESR > 20 mm / h. CRP levels were high (mean, 135.4 ± 84.4 mg / dl; range, 11 - 295 mg / dl) in all patients. Leukocytosis ($\geq 10,200$ WBCs / mm^3) was found in 10 patients (47.6%) and 11 patients (52.4%) had normal WBC count.

Sinus-track cultures yielded 25 isolates in total; 16 were Gram-positive aerobes, nine were Gram-negative aerobes, compared with 21 isolates from bone cultures, including 15 Gram-positive aerobes and six Gram-negative aerobes. A total of 25 and 21 isolates from both sinus-track and bone cultures were recovered from 21 patients, accounting for 1.19 and one isolates, respectively.

The patterns of aerobic bacteria, isolated from the sinus-track and bone specimens, were similar and consisted of *S. aureus*, coagulase-negative staphylococci (CNS), *Enterobacteriaceae* (including *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus spp.*), *P. aeruginosa*, and *Streptococcus pyogenes*. Sinus-track specimen cultures yielded monomicrobial isolates in 17 / 21 (80.9%) cases and *S. aureus* formed the majority in 9 / 17 (52.9%), followed by *P. aeruginosa* 2 / 17 (11.7%). The isolates were polymicrobial in 4 / 21 (19.1%) and no culture showed 'no growth'. Bone cultures allowed isolation and identification of the cause of COM in 20 patients; the other subject had COM demonstrated by bone histopathologic analysis, but no organisms were visualized or isolated from their bone specimens, including aerobic and anaerobic bacteria, *Mycobacterium* species, and fungi. Bone specimen cultures yielded monomicrobial isolates in 19 / 21 (90.5%) cases and *S. aureus* was most common (13 / 19 (68.4%)), followed by *P. aeruginosa* 2 / 19 (10.5%). The isolates were polymicrobial in 1 / 19 (5.2%). Anaerobic bone and sinus-track cultures were done for all patients, but no pathogenic obligate anaerobes were isolated from any culture.

Both specimens grew the same genera and species in 13 patients (61.9%), but three had divergent susceptibility patterns demonstrating different strains of the same species. Thus, concordance between bone and sinus-track was 47.6%.

S. aureus was isolated from the infected bone in 13 patients; two of them (15.4%) did not have *S. aureus* in sinus-track specimens, and only 11 (84.6%) matched exactly with sinus-track cultures. On the other hand, *S. aureus* was isolated from sinus-track specimens, nine in monomicrobial and three in polymicrobial cultures. Looking at *S. aureus* in monomicrobial and polymicrobial COM, the sinus-track specimens were concordant with bone specimens in seven (77.7%) and two patients (66.6%), respectively.

DISCUSSION

Osteomyelitis is well described in the pediatric population and most cases respond to medical measures without lasting sequelae^[12]. The mean age and male / female ratio of the patients in this study are similar to those previously reported in all series^[2, 3, 12, 13] except one^[14]. In this study, ESR and CRP were elevated in most patients and WBC count was normal in 52.4%. These results were also similar to studies by Al Zamil *et al*^[15] and Matzkin *et al*^[3].

COM remains a challenging disease process to define and thus to treat. Bacteriological diagnosis is essential in the choice of treatment regimen^[16]. A sinus-track culture is used commonly and was considered adequate until Mackowiak *et al*^[17], in 1978, reported that bone culture was the most reliable predictor of pathogenic organisms in COM. Their data also indicated that the organism from the bone was growing in the sinus-track in fewer than half of their patients who had *S. aureus* osteomyelitis. Other investigators have extrapolated these results and have advocated culture of material obtained by open biopsy as the most reliable predictor of pathogenic organisms^[9, 18-21]. In contrast to these studies, other studies concluded that the organisms isolated from the sinus-track cultures were similar to those isolated from the bone cultures^[16, 22-24]. However, sinus specimen is readily harvested and used in the preoperative assessment of patients with COM.

This retrospective study confirms that bone culture is the reliable method for the isolation of all bacteria causing COM. Mackowiak *et al*^[17] and Ulug *et al*^[9] have reported that sinus-track cultures were identical to operative cultures in only 44 and 38% specimens respectively. The concordance between sinus-track and bone specimen cultures was approximately 48% in this study. On the other hand, this concordance was 88.7% in study by Mousa^[24] and 70% in Perry *et al*^[22].

Why sinus-tracks that originate from the infected bone do not consistently yield the pathogen responsible for the bone infection is not known^[17]. Previous antibiotic treatment might lead to suppression of the true pathogen and promote colonization of the sinus-track by organisms that are resistant to the antibiotics

Table 1: Demographic and laboratory data of the patients with COM

n	Age in years	Sex	WBCc	ESR	CRP	Path	Site of COM	No. of isolated pathogens		Isolation of pathogen	
								Single	Multiple	Sinus-track culture	Bone culture
1	6	M	7,100	86	196	(+)	Tibia	(+)	(-)	<i>K. pneumoniae</i>	MRSA
2	4	F	22,800	39	81	(+)	Tibia	(+)	(-)	<i>P. mirabilis</i>	<i>P. mirabilis</i>
3	13	M	12,200	86	91	(+)	Tibia	(-)	(+)	<i>E.coli</i> + MRSA	<i>E.coli</i> + MRSA
4	5	F	7,100	60	11	(+)	Humerus	(+)	(-)	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>
5	7	M	14,400	92	110	(+)	Tibia	(+)	(-)	MSSA	MSSA
6	11	M	11,300	52	186	(+)	Tibia+Fibula	(+)	(-)	MSSA	MSSA
7	8	M	14,000	84	168	(+)	Tibia	(+)	(-)	MSSA	No growth
8	12	M	6,950	79	68	Not done	Femur	(+)	(-)	MRS	MRS
9	6	M	14,300	28	40	(+)	Tibia	(+)	(-)	MSSA	MSSA
10	5	F	16,900	92	27	(+)	Tibia	(+)	(-)	MSSA	MSSA
11	2	F	13,100	66	208	(+)	Tibia	(-)	(+)	MSSA+ <i>E.coli</i>	MSSA
12	13	M	6,660	41	210	(-)	Femur	(+)	(-)	MSSA	MRSA
13	6	M	9,270	112	72	(-)	Tibia+Fibula	(+)	(-)	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>
14	9	F	15,900	86	134	(+)	Tibia	(-)	(+)	<i>Strep.pyogenes</i> + <i>P.penneri</i>	MSSA
15	13	M	5,900	28	128	(+)	L4 Vertebra	(+)	(-)	MSSA	MSSA
16	9	M	16,600	71	277	(+)	Tibia	(+)	(-)	MSSA	MSSA
17	15	M	9,680	125	295	(+)	Tibia+Fibula	(+)	(-)	MRSA	MRSA
18	8	F	8,700	72	69	Not done	Tibia	(+)	(-)	MSS	<i>K. pneumoniae</i>
19	9	M	7,400	58	154	(+)	Femur	(+)	(-)	<i>E.coli</i>	<i>E.coli</i>
20	7	M	9,300	79	131	(+)	Tibia	(+)	(-)	<i>E.faecalis</i>	MRS
21	10	M	6,900	61	78	(+)	Tibia	(-)	(+)	MSSA + <i>E.coli</i>	MSSA

M: Male, F: Female, WBCc: Total white blood cell count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Path: Pathology-result, COM: Chronic osteomyelitis, MRS: Methicillin resistant coagulase-negative staphylococci, MRSA: Methicillin resistant *S. aureus*, MSSA: Methicillin sensitive *S. aureus*

being administered. This might also explain the fact that early sinus-track cultures more commonly contained the operative pathogen than those obtained from our patients later in course of their COM.

Our patient population was unique in that all of our patients had post-traumatic or postoperative osteomyelitis. Other studies included patients who had hematogenous osteomyelitis or osteomyelitis due to contiguous spread, such as secondary to diabetic or decubitus ulcers^[18, 21]. In our study, the material for culture was obtained under carefully circumscribed conditions. For example, antibiotics were discontinued at least 48 hours before samples were taken, but other authors have not discussed whether they discontinued antibiotics before obtaining material for culture or not^[25].

Our data indicated that, *S. aureus* was the most common pathogen causing COM in our patient population and this is similar to other studies; however, CNS, *P. aeruginosa* and various Enterobacteriaceae were the agents responsible for osteomyelitis. In this study, no anaerobic infection was encountered. Nevertheless, anaerobic infections of bone are uncommon^[17], but the failure of organisms to grow on anaerobic culture of material obtained does not rule out the presence of anaerobic pathogens. This may indicate a failure in our culture technique. However, tuberculosis should be suspected if routine aerobic and anaerobic cultures from a flowing sinus or bone do not support growth of

any pyogenic bacteria. An important finding was that mycobacteria can sometimes be isolated from sinus-track culture when bone culture, histopathology and clinical examination have all failed to confirm the diagnosis.

Despite the strengths of our study, a few limitations deserve mention. For example, its retrospective nature, the modest sample size and selection bias of patients. Secondary COM is relatively uncommon in childhood and because of this reason our sample size may not be large enough to detect a statistically significant difference between sinus-track and bone cultures. But it has revealed that bone cultures are essential to determine the real causative pathogen in COM.

CONCLUSION

Osteomyelitis is a major medical problem in most countries and a very expensive disease for patient and society because of the involved costs of diagnosis, inpatient and outpatient treatment, rehabilitation, lost productivity, and sequelae. This study shows that if treatment of chronic osteomyelitis (COM) was planned according to the microbiological analysis of material from the sinus-track, it may not result in recovery every time. We found approximately 48% concordance between sinus-track and bone cultures. In other words, antimicrobial therapy guided by antibiograms of bacteria isolated from sinus-track would be inappropriate in 52% of patients with COM and result in treatment failure.

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Case Report

Multifocal Solitary Subungual Glomus Tumors in a Patient with Neurofibromatosis Type 1

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ABSTRACT

We report a case of multifocal solitary glomus tumors in a patient with neurofibromatosis type 1. A 63-year-old female patient presented with severe pain in left ring finger and moderate pain in left little finger for past six years. Clinically, we diagnosed the case as neurofibromatosis type 1 with multifocal solitary glomus tumors. Patient underwent surgery for removal of glomus tumors from the affected two fingers as well as for two nodules in the face for cosmetic

reason on patient's request. Typical pearl-like nodular glomus tumor was visible macroscopically during operation on the left ring finger, but not well defined in the left little finger. Histopathologically, they were glomus tumors. One of the two nodules removed from the face showed typical neurofibromatosis histopathologically and another showed sebaceous lesion. Postoperative follow up was uneventful and pain was relieved completely.

KEYWORDS: neoplasms, neurofibroma, vascular

INTRODUCTION

Neurofibromatosis is an autosomal dominant disorder with two major subtypes: neurofibromatosis type 1, which is the most common subtype and is referred to as peripheral neurofibromatosis, and neurofibromatosis type 2, which is referred to as central neurofibromatosis. Two variants of glomus tumors exist: solitary glomus tumors and multiple glomus tumors, which are also known as glomangiomas or glomulovenous malformations. Each variant has distinct clinical and histopathologic characteristics. Phalangeal glomus tumour is a benign tumor that develops from the neuromyoarterial elements of the glomus body, which is a specialized arteriovenous anastomosis involved in thermoregulation. Control of the function of the arteriovenous anastomoses is mainly neural. Most glomus tumors are localized in the distal phalanx. It is a small tumor with a subungual or pulpar localization and with typical symptoms consisting of the triad of pain, cold intolerance, and very localized tenderness^[1]. Most cases of phalangeal glomus tumors are solitary. Multiple glomulovenous malformations of the skin show autosomal dominant inheritance^[2] and are linked to the chromosome 1p21-22 region^[3]. The abnormalities in the skin consist of cutaneous venous malformations with smooth muscle-like glomus cells. The gene involved in this familial condition has been cloned and named glomulin^[4].

Glomulovenous malformations of the skin are clinically and etiologically different from the sporadic glomus tumors of the distal phalanx. We report a case of multifocal solitary glomus tumors in a patient with neurofibromatosis type 1.

CASE REPORT

A 63-year-old Saudi female patient was referred to our Physical Medicine and Rehabilitation Department, Prince Abdur Rahman Al Suderi Hospital, Sakaka, Saudi Arabia for nerve conduction study with a probable diagnosis of neuropathy. Her presenting complaint was severe pain in the left ring finger and moderate pain in the left little finger for the last six years. Her daily activity was affected due to the severe pain. She had a history of attending various medical facilities in different places without any relief of pain. Clinically, we diagnosed the case as neurofibromatosis type 1 with multifocal solitary glomus tumors. Neurofibromatosis type 1 was diagnosed by following clinical criteria - more than six cutaneous café au lait spots, iris Lisch nodules, axillary freckling, and cutaneous neurofibromas. Glomus tumors were diagnosed clinically by the existence of the three painful symptoms: spontaneous pain, pain on exposure to the cold and pain on pressure (positive Love test). We could not find the characteristic discoloration of nail bed because patient was using henna, a locally popular deep brown cosmetic coloring

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Fig. 1: Bluish purple lesion can be seen in the ring and little finger nail beds

agent for nails. Nerve conduction study for upper limb was normal. Unfortunately we could not perform MRI for this patient. We told her not to use henna again and come back to our department once the henna grows out. She came back after five months for re-evaluation when henna could not be seen anymore. We observed the bluish purple discoloration under the nail beds with nail deformities in the affected fingers (Fig. 1), reconfirming the case clinically as a multifocal solitary glomus tumor in a case of neurofibromatosis type 1. Patient underwent surgery for removal of glomus tumors from the affected two fingers as well as for two nodules on the face for cosmetic reason on patient's request. Typical pearl like nodular glomus tumor was visible during operation (Fig. 2) in left ring finger, but not well-defined in left little finger. Histopathologically, we found that the solitary lesions appeared mostly as solid well-circumscribed nodules surrounded by a rim of fibrous tissue. They contained endothelium-lined vascular spaces surrounded by clusters of glomus cells. The glomus cells were monomorphous

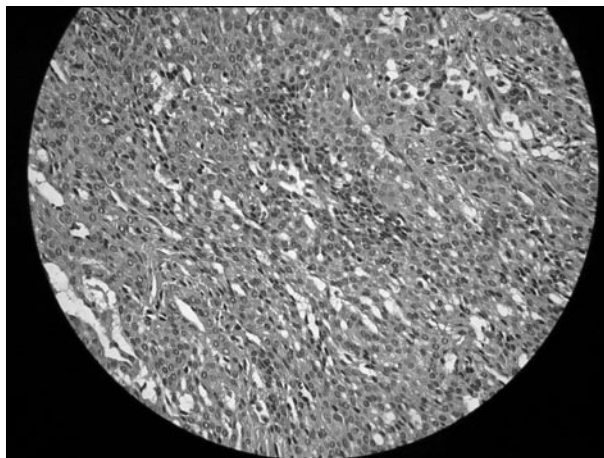


Fig. 3: The glomus cells with monomorphous round and polygonal cells with plump nuclei and scant eosinophilic cytoplasm



Fig. 2: Solitary well circumscribed pearl like tumor can be seen on the dissected flap

round or polygonal cells with plump nuclei and scant eosinophilic cytoplasm (Fig. 3). Findings were similar in both the removed glomus tumors. One of the two nodules removed from the face showed typical neurofibromatosis histopathologically, and another showed sebaceous lesion. Postoperative follow up was uneventful and the pain was relieved completely. Her activities of daily life also improved dramatically.

DISCUSSION

Subungual glomus tumors are usually solitary and the association of multifocal solitary glomus tumors with neurofibromatosis type 1 has only rarely been reported^[5-7].

Multifocal phalangeal glomus tumors in several patients with neurofibromatosis type 1 suggest that this is not an incidental association but that neurofibromatosis type 1 patients have an increased incidence of glomus tumors. Smet *et al* hypothesized that glomus cells are of neural crest origin^[8]. Neural crest stem cells can be isolated from mammalian fetal peripheral nerves. Neural crest stem cells form three different cell types in culture - neurons, Schwann cells, and smooth muscle-like myofibroblasts^[9]. These myofibroblasts are positive for alpha-smooth muscle actin and might be the precursors of the alpha-smooth muscle actin positive glomus cells in the glomus organ of the nail bed. Therefore, it is possible that a second hit in the neurofibromatosis type 1 gene in an alpha-smooth muscle actin positive glomus cell results in a glomus tumor in neurofibromatosis type 1 patients in a similar way as a second hit in a Schwann cell is responsible for a neurofibroma^[8].

Average delay in the diagnosis of glomus tumor is two and half years^[10]. In another study, the time to surgery from the onset of symptoms ranged from six months to 30 years^[11]. In our patient, diagnosis may have been delayed due to the habit of using henna by the patient, camouflaging the characteristic bluish

purple discoloration of nail beds. It is also possible that glomus tumors are not always diagnosed in neurofibromatosis type 1 patients because the symptoms might be attributed to the presence of cutaneous neurofibromas in the same region and resection of the superficial nodules (cutaneous neurofibromas) is insufficient to diagnose and resolve the problem. The intense pain associated with this tumor may even lead to disuse atrophy of the upper limb^[12]. Therefore, it is important to be aware of the possibility of glomus tumors in neurofibromatosis type 1 patients with pain in the fingers because surgical intervention to remove the glomus tumor cures the pain as well as improves the quality of life.

CONCLUSION

Intense pain in multiple fingers in neurofibromatosis type 1 patients should alert clinicians about the possibility of multifocal glomus tumors which are completely curable with surgical excision.

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Case Report

Laparoscopic Appendectomy in the Third Trimester of Pregnancy: Report of Two Cases and Description of Technique

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ABSTRACT

Acute appendicitis is the most common cause of acute abdomen during pregnancy. Its prevalence is equally distributed throughout the three trimesters. Although laparoscopic appendectomy is a safe and effective procedure for management of acute appendicitis, data about the feasibility and safety during pregnancy are limited, especially the role of laparoscopic appendectomy

in the third trimester. In fact, some authors have advocated a gestational age of 28 weeks to be the upper gestational limit for successful completion of laparoscopic surgery. In this paper, we present two cases of successful laparoscopic appendectomy during the third trimester without complication to mother or fetus along with a description of our operative technique.

KEYWORDS: appendicitis, laparoscopic surgery, operative technique

INTRODUCTION

Acute appendicitis is the most common cause of acute abdomen in pregnancy. The prevalence is equally distributed throughout all trimesters with an incidence ranging between 0.05 to 0.13%^[1].

The objective of this case report is to demonstrate that laparoscopic surgery in the third trimester is feasible and can be performed safely^[2,3]. This is contrary to the belief by some authors that the 26th to the 28th week should be the upper gestational limit for successful completion of laparoscopic surgery^[4].

There are limited data in the English literature on third trimester laparoscopic appendectomy. Most publications on laparoscopic surgery in the third trimester of pregnancy include either single case reports or small case series involving two to four cases^[3]. In this paper we present two cases of successful laparoscopic appendectomy in the third trimester with a description of our operative technique.

CASE HISTORY**Case 1**

A 39-year-old woman was admitted to our hospital with sudden onset right lower quadrant abdominal pain. Gestational age was estimated to be 30 weeks. There were no associated symptoms and there was no vaginal bleeding.

The patient was afebrile and her vitals were stable. Her physical examination showed a gravid uterus along with right lower quadrant tenderness and guarding. The clinical diagnosis was acute appendicitis.

Laboratory evaluation showed a white blood cell count of $14.2 \times 10^9/l$, and her ultrasound was equivocal.

A diagnostic laparoscopy was performed. There was torsion of appendices epiploica around the cecal area which was excised along with excision of a normal looking appendix. The surgical procedure that we have performed was as per the guidelines of the Society of American Gastrointestinal Endoscopic Surgeons (SAGES). The procedure was performed under general anesthesia. The patient was positioned in supine decubitus and tilted 20 to 30 degrees to the left. This position frees the vena cava from compression and exposes the appendicular area. Compression devices were placed on both lower extremities.

Foley catheter and orogastric tube were placed and the abdomen was draped using sterile technique. Antibiotic prophylaxis was administered intravenously at the time of induction.

The uterine fundus was palpated and a 10 mm camera port was inserted using the open technique 3 - 4 cm above the superior margin of the uterus. A 10 mm working port was inserted under visual guidance of a

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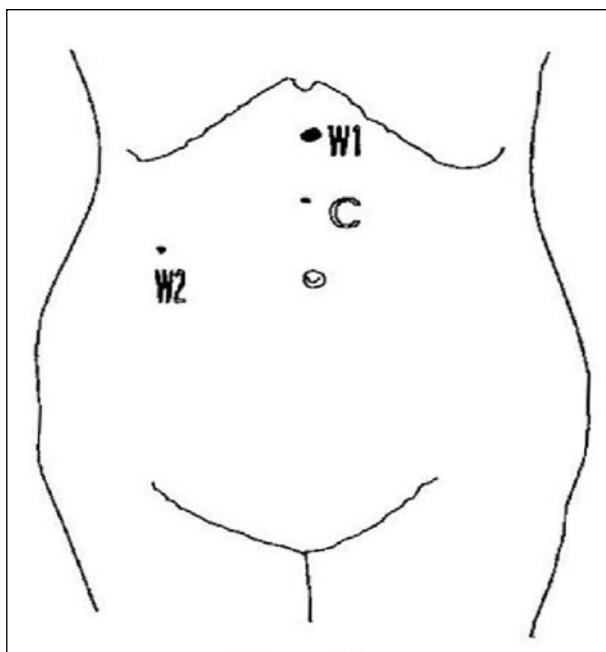


Fig. 1: Port sites for patients in the third trimester. A 10 mm camera port (C), was inserted 3 to 4 cm above the superior margin of the uterus. A 10 mm working port (W1) was inserted below the xiphoid process. A 5 mm sub costal working port (W2) was inserted at the right anterior axillary line.

30 degree scope below the xiphoid process. Another 5 mm subcostal working port was inserted at the right anterior axillary line (Fig. 1). The CO₂ pressure was maintained between 8 – 12 mmHg, trying to maintain the minimum level required to obtain a correct working space. Care was taken to minimize manipulation of the gravid uterus.

The mesentery of the appendix was secured with endoclips. Once the base was reached, two pre-tied chromic catgut loops were applied and the appendix was cut between both loops with scissors. The organ was delivered through the subxiphoid port. The right lower quadrant was irrigated with saline. Hemostasis was secured and the base of the appendix was inspected one last time to recheck the security of the applied endoclips.

The ports were removed under direct vision, the pneumoperitoneum was evacuated and the rectus sheath of the optical port was closed using 2/0 PDS. Skin was closed using subcuticular absorbable suture.

An ultrasound examination was repeated before the patient's discharge which confirmed fetal vitality. She was discharged home on the second postoperative day.

Pathological examination of the specimen was consistent with torsion of appendices epiploica with a histologically normal appendix. The patient did not require tocolytics and delivered vaginally at term.

Case 2

A 29-year-old woman was admitted to our hospital with generalized abdominal pain of one day duration which later localized to the right flank area. Gestational age was estimated to be 28 weeks. There were no symptoms associated with the abdominal pain and there was no vaginal bleeding. The patient was afebrile and her vitals were stable. Her physical examination showed a gravid uterus along with right lumbar tenderness and guarding. The clinical diagnosis was acute appendicitis.

Laboratory evaluation showed a normal white blood cell count and her ultrasound was equivocal.

A laparoscopic appendectomy similar to the one described above was performed without incident. Findings were that of an acutely inflamed retrocecal appendix with mild intraperitoneal fluid reaction.

An ultrasound examination was repeated before the patient's discharge which confirmed fetal vitality. She was discharged home on the third postoperative day. Pathological examination of the specimen was consistent with an acutely inflamed appendix. The patient did not require tocolytics and delivered vaginally at term.

DISCUSSION

Acute appendicitis is the most common non-obstetric cause of acute abdomen during pregnancy. The prevalence is evenly distributed throughout all trimesters^[5]. The diagnosis of acute appendicitis in pregnant woman is more difficult than it is in other clinical settings, as the physiological and anatomic changes in pregnancy can obscure the condition^[6,7].

Delayed treatment of acute appendicitis increases the rate of maternal complication or fetal loss^[6-8]. Therefore, early and aggressive treatment of clinically suspected appendicitis in pregnancy is justified. The laparoscopic approach has become more widely accepted as safe and effective and has become the standard of care at some institutions in all trimesters of pregnancy^[9].

Limited data exists on third trimester laparoscopic appendectomy and some authors recommend the second trimester as the safest for performing laparoscopy^[10]. The major advantages of the laparoscopic approach to appendectomy in the third trimester are better visualization resulting in limited uterine manipulation and minimal morbidity for a negative exploration.

Rollins *et al* reported that as many as 41% of the appendices removed during pregnancy for clinically suspected appendicitis, using the conventional open approach, were found to be normal^[7]. Reduced intra-operative uterine manipulation may lead to decreased postoperative uterine irritability, premature labour,

and premature delivery, seen in up to 40% of third trimester cases in the past^[11-13].

Other potential advantages of the laparoscopic approach to appendectomy in the third trimester include an earlier return of gastrointestinal function, earlier ambulation, decreased incidence of deep vein thrombosis, decreased hospital stay and a quicker return to routine activities^[14]. Laparoscopy may be associated with lower rates of wound dehiscence, infection, hernia, less pain and decreased narcotic use compared with patients undergoing conventional appendectomy. Reduction in narcotic use reduces fetal narcotic depression and maternal hypoventilation which can lead to fetal acidosis^[13-15]. Improved cosmesis is an added benefit for the body conscious patient.

Major concerns about laparoscopic appendectomy have focused on the effects of increased intra abdominal pressure and fetal acidosis during CO₂ pneumoperitoneum. Hunter and colleagues meticulously investigated the physiological impact of a CO₂ pneumoperitoneum in these clinical settings. Their conclusions were that a CO₂ pneumoperitoneum created minimal impact on the patient and fetus when an intra abdominal pressure of 15 mmHg or less was used^[16].

Nevertheless, in 1998, SAGES published a list of guidelines which included the use of minimal pneumoperitoneum pressure of 8 – 12 mmHg, with serial arterial blood gas analysis along with end tidal CO₂ monitoring in an effort to diminish the hemodynamic effect of the pneumoperitoneum^[15].

Direct uterine injury during trocar placement has been reported during laparoscopy without fetal loss^[17]. These injuries can be avoided by the use of open technique in the establishment of pneumoperitoneum and the careful introduction of additional trocars under direct vision^[10,15,18].

Premature labour and delivery are significant concerns during the third trimester. Facilities capable of managing the premature infant should be immediately available and close cooperation between the general surgeon, the anesthesiologist and obstetrician is essential.

CONCLUSION

According to published statistics and also our own experience, laparoscopic appendectomy should be the procedure of choice in all trimesters of pregnancy. The advantages of laparoscopic surgery include better intra-operative visualization and exposure, less uterine manipulation, reduced narcotic use and hence less fetal depression, early return of bowel function, early ambulation and shorter postoperative stays. Finally,

close cooperation between the general surgeon, obstetrician and anesthesiologist is an important determinant of a successful maternal – fetal outcome.

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Case Report

Autoimmune Adrenal Insufficiency Antedates the Diagnosis of SLE, Does It Really Matter?

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ABSTRACT

Coincidence of primary adrenal insufficiency and systemic lupus erythematosus (SLE) is a rare occurrence. Several pathological processes have been suggested to explain the association but variability of the reported cases suggests a multi-factorial etiology, in which tissues and cells are damaged by pathogenic autoantibodies and immune complexes. Association of anticardiolipin antibodies

with thrombosis is well-established. In clinical settings, the symptoms of adrenal insufficiency are masked by multi-systemic nature of SLE and manifestations vary according to tissues affected. We report a case of a young girl, where her autoimmune adrenal insufficiency antedated the diagnosis of SLE by two years with absence of antiphospholipid antibodies.

KEY WORDS: anticardiolipin, antiphospholipid, autoimmune adrenalinsufficiency, SLE

INTRODUCTION

The clinical spectrum of Addison's disease has changed dramatically over the last 30 years, and autoimmunity is now the most common cause of primary adrenal insufficiency^[1]. Adrenal insufficiency is characterized by weight loss, fatigue, low blood pressure, and sometimes darkening of the skin. This is a consequence of hypocortisolism, and in some cases hypoadosteronism^[1,2]. Autoimmune mechanism is one of the etiologies of hypocortisolism. About 50-60% of patients will develop additional autoimmune endocrinopathies during their life as manifestations of polyglandular syndromes type 1 and 2^[3,4]. The treatment is usually hormonal replacement with glucocorticoids and mineralocorticoid.

Systemic lupus erythematosus (SLE) is occasionally accompanied by autoimmune disorders of endocrine glands, most commonly the thyroid, but rarely the adrenal glands^[3]. Adrenal failure has been described in adults with SLE^[5,6], and in three children^[7] and in several adults with antiphospholipid syndrome^[3,4,8], a condition that occurs most frequently in patients with SLE. However, our case is very unique in describing the co-existence of autoimmune adrenal insufficiency prior to the diagnosis of SLE and in absence of antiphospholipid antibodies. To the best of our knowledge this has not been reported earlier in the literature.

CASE REPORT

A 20-year-old Kuwaiti girl reported to the outpatient department of internal medicine with the chief complaint of black spots over the tongue and the gingiva (Fig. 1) that kept increasing in color over a 12-month period. She also reported lethargy and muscle weakness of a few months duration. There was no history of skin rash, joint pain or connective tissue disease symptoms.

Her past medical history revealed pulmonary tuberculosis at age of six years, which was treated successfully with multiple anti-tuberculous drugs for an appropriate length of time. No family history of connective tissue disease or endocrinopathy could be elicited.

The physical examination revealed a thin, averagely built young lady with a BMI of 21. Her BP was 90/60 mmHg with no postural hypotension. The skin was hyperpigmented over creases of both hands (Fig. 2), old scars over the feet (Fig. 3) and hyperpigmented spots over the tongue and gingiva. The rest of systemic examination was normal.

The patient was admitted to the internal medicine ward and investigated thoroughly. Her CBC, thyroid function, renal and liver profiles were within normal limits. Her serum electrolytes revealed mild hyponatremia of 121 mmol/l and K⁺ of 4.4 mmol/l.

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Fig. 1: Hyperpigmented tongue and lips



Fig. 3: Hyperpigmented old scars on the dorsum of the feet

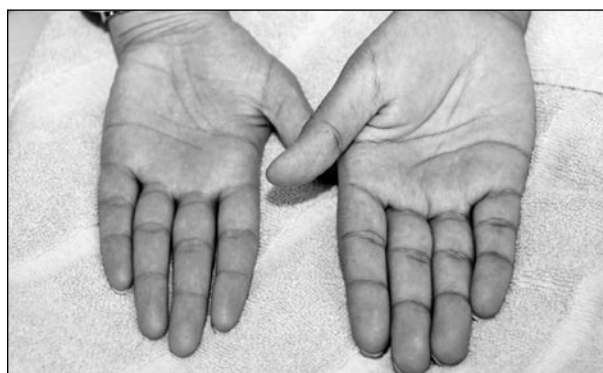


Fig. 2: hyperpigmented creases of the hand (patient's hand is on the right side)

Short synacthen test was carried out and showed S-cortisol level of 203 nmol/l (normal 140 - 550 nmol/l) at time zero, 240 nmol/l at 30 minutes and 205 nmol/l at 60 minutes. Her S-ACTH level at 8 am was 1250 pg/ml (normal: 10 - 90 pg/ml) and adrenal autoantibodies were positive (by indirect fluorescent antibody technique).

However, her serum aldosterone was normal. Serum FSH, LH and estrogen levels were not done because she did not have menstrual disturbances. Her PPD skin test was positive with an 18 mm induration, but CT scan abdomen showed normal adrenals. Therefore, she was diagnosed to have an autoimmune adrenal insufficiency with preservation of mineralocorticoid axis.

She was started on oral glucocorticoid, in divided doses and her lethargy improved dramatically. She also received education about her disease and was advised to adjust the doses of cortisol during times of stress, and then discharged home.

Her follow-up in outpatient clinic was regular and she showed excellent drug compliance. Her symptoms had improved markedly and the cutaneous hyperpigmentation had disappeared. The domestic follow-up of her BP showed systolic of 100 - 120 mmHg and diastolic of 60 - 80 mmHg. Repeated serum electrolytes were normal and calcium and vitamin D supplement were prescribed.

Two years later, she developed a different rash with joint pain, morning stiffness, color changes of fingers upon exposure to cold and had ulceration on the right index finger tip. She also noticed painless oral ulcers, moderate loss of hair along with weight loss within previous one month and amenorrhea.

She was ill with a temperature of 38.3 °C. The rashes had a butterfly distribution on the face and discoid lesions all over the body with central scarring and jet black hyper-pigmentation. There was multiple, symmetric, large and small joint involvement with restriction of movement of ACR functional grade II. Multiple mouth ulcers were found especially over the hard palate.

Laboratory investigations showed an elevation of erythrocyte sedimentation rate to 97, hemoglobin (80 gm/l), platelet ($180 \times 10^9/l$), WBC ($5 \times 10^9/l$). Prothrombin time and activated partial thromboplastin time were normal, with positive ANA and anti-ds DNA antibody. Other investigations include normal level of IgG anticardiolipin antibody and a positive direct Coombs' test. Urine examination revealed moderate proteinuria (total urinary protein 2.4 gm/24 hours). Renal biopsy was not possible at that time. She was diagnosed as a case of SLE and started on prednisolone 1 mg/kg body weight in three divided doses. Improvement occurred with prompt relief of joint pain and healing of oral ulcers and skin rashes. There was a gradual increase in appetite with weight gain, correction of anemia, restoration of menstruation to normal and no proteinuria. Dose of prednisolone was then gradually tapered to 7.5 mg daily, (5 mg in the morning and 2.5 mg at night). The patient was sustained in a remission during the 10-month follow-up.

DISCUSSION

Several reports have described the association between acute adrenal insufficiency (adrenocortical hemorrhage or hemorrhagic infarction) and antiphospholipid antibody syndrome^[3,4,5,9]. Our case was diagnosed with autoimmune adrenal

insufficiency, as proved by hyper-pigmentation, hypotension, extreme fatigue and low serum cortisol level (203 nmol/l) which failed to rise one hour after intravenous injection of 0.25 mg co-syntropin two years prior to her presentation with features of SLE (fulfilling the ARC criteria) that manifested as malar rash, discoid rash, photosensitivity, painless oral ulcers, arthritis, hemolytic anemia and renal involvement.

As SLE is a multi system disorder, many of the clinical features are common with adrenal insufficiency. Among 20 reported cases with positive anticardiolipin antibodies with adrenal failure, only four cases developed features of SLE^[5,9].

In our case, the autoimmune adrenal insufficiency antedated the clinical diagnosis of SLE. This could be due to the fact that, the immune destruction of the adrenals started earlier than other tissue in the body or long term steroid therapy for autoimmune adrenal insufficiency may have masked the clinical presentation of SLE. Another explanation may be that many of the non-specific clinical features of SLE are common with adrenal insufficiency. This *per se* can create a great confusion in clinical diagnosis in the beginning, but with close and careful follow-up, definite diagnosis can be made easily, as other symptoms appear with time. This is what happened with our patient. Moreover, it is very unlikely that these two clinical conditions are not related pathologically and only co-existed in the same patient.

The etiology of hypoadrenalism in SLE is unknown, but proposed mechanisms may be adrenal vascular thrombosis and infarction, hemorrhage due to abnormal coagulation, vasculitis and a direct organ specific autoimmune insult^[2,4,6,8]. Early reports of the association suggested the presence of antiphospholipid antibodies (APLA) in these patients, and hence the adrenal failure has been related to their presence^[3,4,6] but APLA were not found in our patient despite being diagnosed with SLE.

In SLE, adrenal involvement may be the first clinical manifestation of this syndrome, whereas a few patients may have history of adrenal insufficiency in the past^[2,8]. In some cases of adrenal damage due to hemorrhage, incomplete destruction of adrenal cortex may leave enough residual function to prevent acute adrenal crisis, with later development of chronic adrenal insufficiency^[2].

The association between SLE and adrenal insufficiency has been described earlier in the literature. In all reported cases, the diagnosis of adrenal insufficiency was made after the diagnosis

of SLE^[5,6] and in some cases, both conditions have been described simultaneously^[6,9-11]. We describe for the first time in the literature, autoimmune adrenal insufficiency antedating the diagnosis of SLE with negative APLA. This proves the hypothesis of the presence of other pathological mechanisms rather than APLA, in this association.

CONCLUSION

This case suggests the need for increased suspicion of SLE in patient with adrenal insufficiency and systemic complaints. This clinical suspicion should be high when patient with adrenal insufficiency present with arthralgia, skin rash, anemia and raised ESR. To confirm the diagnosis, ANA and anti-ds DNA should be done, but APLA may not be found in these patients. Therefore, we advise careful follow up of such patients since they may evolve into connective tissue disease.

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Case Report

Macroinvasive Papillary Thyroid Carcinoma Presenting as Internal Jugular Vein Tumor Thrombus

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ABSTRACT

Papillary thyroid carcinoma with massive invasion into the great veins of the neck and mediastinum has rarely been reported and is thought to have a poor prognosis. But multimodal therapeutic approach comprising of surgery, radioiodine and external beam radiotherapy may

give best results for patients in whom thyroid cancer is occluding the great veins.

Here we report successful management of a case of papillary thyroid carcinoma with extensive invasion into the left internal jugular vein.

KEY WORDS: metastatic thyroid carcinoma, thyroid neoplasm

INTRODUCTION

Microscopic vascular invasion is well recognized in thyroid cancer particularly in the follicular and poorly differentiated histological types^[1,2]. However massive invasion of papillary thyroid carcinoma into the great veins of the neck is rare. Management of these patients is challenging as they typically present with advanced and rapidly progressive disease. We describe the clinicopathological finding and surgical management of a case of papillary thyroid carcinoma with extensive invasion into the left internal jugular vein (IJV).

CASE REPORT

A 47-year-old Philippino lady, not known to have any previous medical problems, presented with a painless firm swelling in the left side of the neck of six months duration and past history of right thyroid lobectomy two years ago in an overseas hospital. There was no operative or pathological report available. On physical examination there was a tender swelling, 2 x 2 cm, deep to lower third of left sternocleidomastoid muscle and multiple painless firm mobile discrete upper and lower deep cervical lymph nodes. There was no facial edema or any dilated veins over chest wall. Patient was clinically and biochemically euthyroid.

Color Doppler sonography showed presence of multiple hypoechoic hypovascular nodules in left

thyroid lobe. The largest of them measured 15 mm, exhibiting a homogeneous hypoechoic texture with clear border and multiple enlarged cervical lymph nodes along the left jugular chain. The left IJV was seen totally occluded above the subclavian vein being filled with large expanding soft tissue thrombus that exhibited color flow signals within. Computed tomography (CT) scan confirmed the tumoral thrombus obstructing the IJV with dilated collaterals at the surface of the left lobe of the thyroid (Fig. 1, 2).

Ultrasound guided fine-needle aspiration cytology (FNAC) of left thyroid lobe and left cervical lymph nodes revealed feature of thyroid papillary carcinoma with cervical lymph node metastasis.

At operation we found tumor in the left thyroid lobe and the superior thyroid vein was dilated, tortuous and full of malignant mass. The left IJV also had a pedunculated tumor mass blocking the vein. It was about 4 cm long and partly attached to the wall of the vein (Fig. 3, 4). Left thyroid lobectomy and modified block dissection involving levels 2, 3, 4, 5A, 6 with excision of IJV from the level of hyoid bone to the lower end of internal jugular vein was performed. The left accessory nerve and sternocleidomastoid muscle were preserved. The postoperative course was uneventful.

Pathologic examination showed multifocal papillary carcinoma, 0.1 to 1.3 cm, with no extra-thyroid extension (Fig. 5). There was metastasis

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Fig. 1: Sagittal CT reformat showing thrombosed jugular vein (asterisk) and partially thrombosed superior thyroid vein (hollow arrow)

within all removed lymph nodes; levels 2, 3, 4, 5A, 6; and IJV invasion with malignant thrombus (Fig. 6). Six weeks after operation, whole body iodine 131 scanning showed two metastatic foci of intense I 131 accumulation in the chest and abdomen. Patient is now a candidate for radioactive iodine (RAI) ablation and thyroxine supplementation.

DISCUSSION

Thyroid carcinoma usually presents as a painless thyroid nodule and has low morbidity and mortality. Thyroid cancer may show microscopic vascular invasion but rarely causes tumor thrombus in the IJV or other great veins of neck^[1]. Only 29 cases have been documented in the literature until April, 2008^[2].

Follicular and Hurthle cell carcinoma are most common pathological type of thyroid carcinomas that invade cervical veins and possess angio-invasive features. Our case was of the papillary type. It is uncommon to have micro-invasion and macro-invasion of the neck veins is even rarer^[1].

According to Graham, Kaufmann was the first to report a case of thyroid cancer thrombi in 1879 at autopsy; the tumor was found to extend into the jugular, subclavian and innominate veins on both sides^[3].



Fig. 2: Axial CT showing thyroid nodule (asterisk) and filling defect of the tumoral thrombus within the internal jugular vein

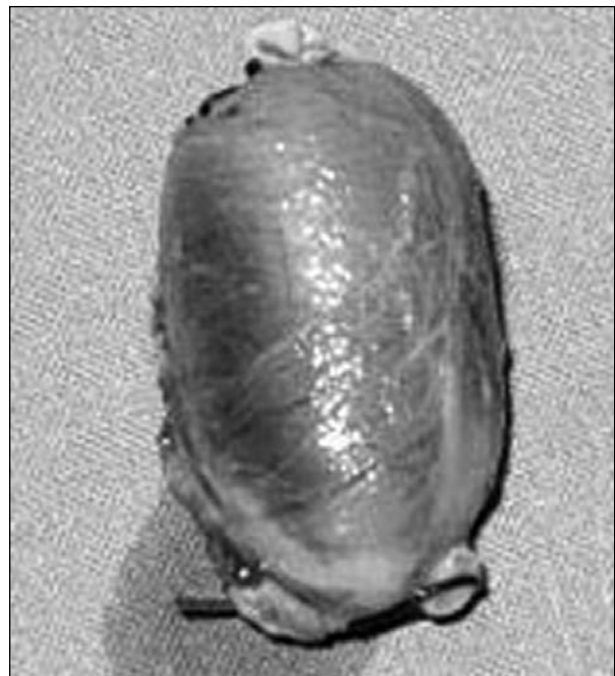


Fig. 3: Distended internal jugular vein with thrombus

The symptoms and signs of a tumor thrombus in IJV and other great veins depend on site and degree obstruction of the lumen. The most common clinical manifestation of such condition is dilated veins of the neck. Because the IJV is located deep to the sternocleidomastoid muscle, a typical palpable cord is not a common presentation of thrombosed IJV. In the present case, patient complaint was left neck pain with palpable mass, without signs of dilated veins over the neck^[4].

The common causes of IJV thrombosis are previous catheterization, trauma, radiotherapy, neck surgery, and hypercoagulation conditions. When

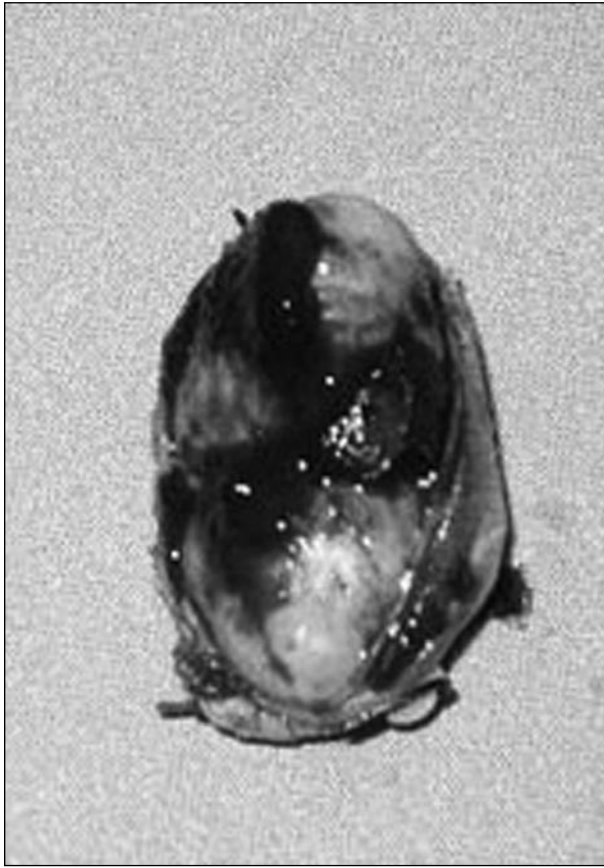


Fig. 4: Opened internal jugular vein and tumor thrombus within

IJV obstruction is found without obvious cause, compression by thyroid enlargement and infiltration by thyroid carcinoma should be considered in the differential diagnosis^[5].

Color Doppler ultrasound may be helpful, especially for excluding thrombus in the IJV. But the structures deep to the mandible and the clavicle are difficult to scan, and SVC may be obscured by osseous structures or lung parenchyma^[6]. CT venography has the advantage over digital subtraction venography in its ability to evaluate the proximal extent of obstruction or thrombosis. The advantage of MRI over CT and ultrasound are a superior soft tissue contrast, and the fact that intravenous contrast is unnecessary. Also Gallium-67 scintigraphy has been used successfully in diagnosing tumor thrombus in a patient with anaplastic thyroid cancer^[7].

Management of these patients is challenging as they typically present with advanced and rapidly progressive disease. Complete resection is recommended where possible to reduce tumor burden. The presence of massive intravascular invasion should not be a contraindication for resection to palliate impending SVC obstruction^[8]. Without surgery the prognosis is bleak and death follows from tumor embolism or obstruction of the right atrium^[9]. During segmental vein resection, the involved vein is ligated before handling to prevent tumor embolization^[10].

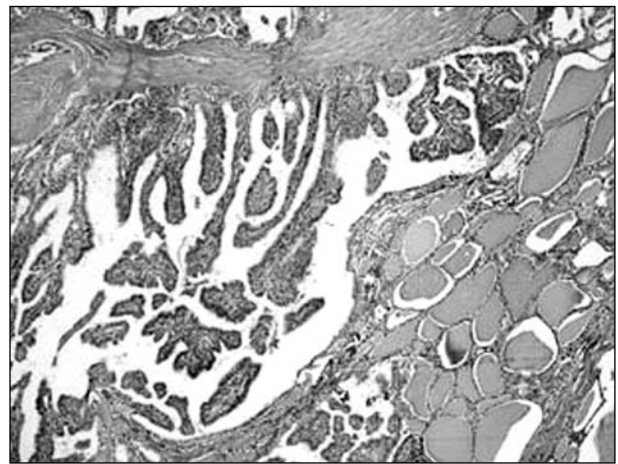


Fig. 5: Microscopic picture of the thyroid with papillary carcinoma



Fig. 6: Microscopic picture of the internal jugular vein completely occluded by the tumor

Surgery should be complemented with radioiodine in iodine-avid tumors as this may reduce the risk of recurrence. The value of external beam radiotherapy (EBRT) in the management of thyroid cancer remains controversial because published data are conflicting and there are no prospective randomized controlled trials. There is good evidence that EBRT improves local control in patients with gross macroscopic residual disease following surgery^[11].

Although there was no extra-thyroid extension and complete resection of the tumor was done, our patient is still in the high risk group. Final TNM categorization was stage IV (T2 N1 M1, >45 years). We are following this patient carefully for RAI ablation response and thoroughly checking for recurrence.

CONCLUSIONS

Papillary thyroid carcinoma with massive invasion into the great veins of the neck and mediastinum has rarely been reported. But every patient with spontaneous IJV thrombosis must undergo careful history and complete physical examination and a thorough investigation to exclude infiltration from thyroid carcinoma as a differential diagnosis.

Radical resection of involved venous segment with thyroidectomy and modified block neck dissection is indicated to achieve better local control and to improve the rate of survival.

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Case Report

Late-Onset Chylothorax after a Pneumonectomy for Lung Cancer: A Case Report

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ABSTRACT

Chylothorax is a relatively rare complication associated with thoracic surgery. It tends to occur in the early postoperative period. The prevalence ranges from 1 - 2%, and without treatment, the mortality rate is around 50%. Chylothorax after a pulmonary resection is usually diagnosed within three days after surgery. Only a few

cases of delayed diagnosis have been reported in literature until now and almost all of them have been reported to occur within 15 days of surgery. Early recognition and prompt treatment are essential. We report a case of delayed onset chylothorax after pneumonectomy with literature review.

KEY WORDS: chylothorax, pneumonectomy, thoracic surgery

INTRODUCTION

Pneumonectomy or removal one of lung, is performed for management of various benign and malignant diseases. This is very stressful situation associated with anatomic and physiologic changes that may result in severe complications^[1,2]. Complications are usually cardiovascular or pulmonary in origin and rarely may involve the pneumonectomy space, oncologic, neurologic or gastroesophageal system^[2,3]. Delayed onset chylothorax after pneumonectomy is extremely rare and only few cases are reported in literature. The etiology, pathophysiology and clinical presentation of chylothorax are reviewed and factors that may aid diagnosis are discussed.

CASE HISTORY

A 66-year-old male had been diagnosed as late stage non-small-cell carcinoma of right lung. After neoadjuvant chemotherapy the tumor was down staged. Right pneumonectomy with systematic mediastinal lymph node dissection was performed because of tumoral invasion of hilar structures. He was staged T2N0M0 (stage1B). After an uneventful postoperative course, the patient was discharged.

He was seen after 10 and 30 days of discharge. Physical, laboratory and radiologic findings were normal at that time. Fourty-four days after his surgery, he was admitted to emergency department with notable shortness of breath. His family had noticed

a few isolated episodes of fainting but he had not mentioned about them.

On examination, he was in a respiratory distress. He had moderate tachypnea. Chest examination revealed decreased breath sounds on right with dullness on percussion, left lung was normal. Cardiac evaluation was normal except for mild tachycardia. The rest of the examination was unremarkable.

Chest radiogram revealed expected post-pneumonectomy changes with an air fluid level on right hemithorax (Fig. 1). Leucocytosis (20,000) and mild hypoalbuminemia (2.4 g/dl) were found on blood analysis. Blood gas analysis revealed respiratory acidosis with pH 7.21, pCO₂ 68.5 mmHg, pO₂ 74.5 mmHg and O₂ of saturation 91.5%.

Thoracentesis yielded a milky effusion characteristic of chylothorax. Analysis of the pleural fluid revealed increased triglyceride levels, suggesting the presence of chyle (cholesterol 95 mg/dl, HDL 7 mg/dl, triglyceride 698 mg/dl, VLDL 140 mg/dl). He was diagnosed as delayed onset chylothorax. An intercostal tube was inserted to decompress post-pneumonectomy space. Dyspnea was relieved, fever subsided and patient felt better.

Total parenteral nutrition was instituted with complete cessation of oral intake. Albumin levels reached acceptable levels by supplemental albumin concentrates. Leucocytosis decreased to 11,900/ml after drainage. Chest radiogram (Fig. 2) after decompression

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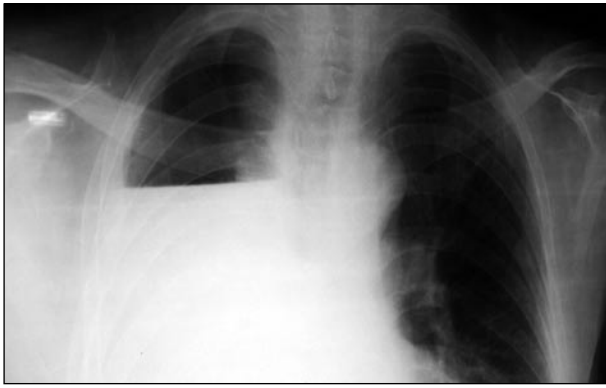


Fig. 1: Chest radiograph taken on admission revealed expected anatomic changes with rising fluid level at second rib on right side.



Fig. 2: Chest radiograph after decompression revealed loss of air fluid level line appearance with mild mediastinal shift to right side

revealed loss of air fluid level line appearance with mild mediastinal shift to the right side. Blood gas results were acceptable for pneumonectomy

Daily blood count and biochemical values were within normal range on following days. Respiratory distress was not obvious. Cultures of pleural fluid revealed no bacterial growth. Daily pleural fluid drainage was 150 - 200 ml with serous appearance. Decreasing daily drainage, improvement in general status, acceptable blood gas analysis results and higher albumin levels prompted us to adopt a conservative approach. But hospitalization course was complicated with an epileptic attack. Neurologic examination revealed cerebral atrophy associated with narrowed carotid lumen. Cerebral metastasis was uncertain on radiological evaluation.

On the 12th day of hospitalization when sitting in bed, he suddenly developed dyspnea followed by cardio-pulmonary arrest. Although we performed resuscitation he could not be revived. The cause of sudden death was obscure because his family seemed unwilling to approve autopsy. Nevertheless a few cases of sudden death after pneumonectomies were reported in literature and thromboembolic events were usually blamed in the etiology.

DISCUSSION

Lung cancer is one of leading cause of death in developed countries. Although there is improvement in chemotherapy and radiation therapy, surgery is still the best solution for better survival. Resection is indicated in stage 1, 2 and some 3 non-small cell lung cancer. Pneumonectomy is one of the resection options with tumors involving main bronchus and pulmonary artery or extension across the major fissure^[3,4].

Most of complications of pneumonectomy are pulmonary or cardiovascular in origin. Less frequently oncologic gastroesophageal and neurologic morbidity is encountered in practice^[3,4]. Traumatization of thoracic duct and tributaries usually leads to accumulation of

a large amount of lymphatic fluid in thoracic cavity. Various invasive and surgical procedures of thorax and neck, cancer invasion, direct or indirect trauma to the duct may result in damage to the thoracic duct^[5].

On the other hand, chylothorax after a pulmonary resection is relatively rare but may lead to respiratory, hemodynamic, metabolic, immunologic or nutritional disturbances^[4,5]. The prevalence ranges from 1 - 2%, and without treatment mortality rate is around 50%. Chylothorax after a pulmonary resection is usually diagnosed within three days after surgery because oral intake usually starts on the first postoperative day^[6].

During the convalescence period the diagnosis is more difficult. Symptoms and findings are usually non-specific and can easily be overlooked. Dyspnea, cough, and chest discomfort are frequently observed symptoms. Pleuritic chest pain and fever are uncommon because chyle is not irritant to the pleural surface. Chylic fluid accumulation in pneumonectomy cavity may cause mechanical compression of contralateral lung and mediastinal structures and compromise pulmonary and cardiovascular function^[5,7]. Deterioration of nutritional status makes the patient more susceptible to infection. Dehydration is also considerable in some cases^[5,7].

Radiologic findings are not specific for chylothorax. Unexpected accumulation of fluid into the pleural cavity in the postoperative period should raise suspicion for hemorrhage, infection, or development of a chylothorax^[3,4].

Decision of thoracentesis is the cornerstone and diagnosis can be verified *via* fluid analysis. Early recognition does not only prevent further deterioration of patient but the less invasive therapeutic modalities may be more appropriate to treat this condition^[5].

Pleural fluid cholesterol / triglyceride ratio of less than 1 and triglyceride level greater than 110 are chyle characteristics^[3]. Suspicion should arise when there is excessive tube drainage over 72 hours after surgery.

Pleural fluid analysis usually reveals the diagnosis but if in doubt lipoprotein analysis demonstrating chylomicrons can confirm diagnosis^{3,5}.

Postpneumectomy chylothorax is a rare but serious complication. It needs prompt diagnosis and intervention. Non-operative and operative approaches depend on the situation and surgeon's preference^{1,5,8}. Non-operative approach includes drainage of pleural cavity, enteral rest and total parenteral nutrition until chylic fluid drainage ceases^{1,5}. Recently, octreotide, a long acting somatostatin analog, administration has been shown to yields some benefit to reduce thoracic ductal flow⁹.

If the non-operative approach fails surgical intervention is indicated. Leakage for more than five days at the rate of 1.5 l/day, leakage persisting over 15 days and deterioration of nutritional and immunological status of the patient are indications for operation^{3,10}. Once the oozing site is identified, the leakage can be treated with suture, clips, fibrin glue, or talcage¹¹.

This case report is noteworthy in several respects. First, this is one of the late onset cases that developed chylothorax 45 days after the operation. Presenting symptoms were non-specific to arouse early suspicion. Chest radiograph revealed expected anatomic changes after operation. Unfortunately, in slowly progressing cases radiologic findings are usually silent. Except leucocytosis blood count was normal. The relation between leucocytosis and chylothorax is not clear. Interestingly, preserved total plasma protein values and mildly decreased albumin concentration supported the delayed onset of this condition. We did not apply any test to assess his nutritional status but oral intake before and after hospitalization was satisfactory. Mediastinal lymphoid tissue dissection was performed for staging. It is difficult to see thoracic duct with naked eye during operation and trauma to the duct may be easily overlooked. Stopped oral intake a day before operation decreased lymph flow and this might have lead to difficulties in recognizing the oozing of chyle.

Lastly, late onset chylothoraces may result due to eradication of the duct by residual tumoral growth after operation.

CONCLUSION

Chylothorax is a rare but life-threatening complication. Early recognition and prompt treatment is essential. Although radiologic and laboratory findings are normal, any symptom developed after sleeve lobectomy must be considered important and has to be investigated.

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Case Report

Thyroid Hemiagenesis: Case Report and Review of Literature

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ABSTRACT

Thyroid hemiagenesis is a rare embryological condition in which the left lobe is usually absent. The remaining thyroid lobe may present as benign adenoma, multinodular goiter, hyperthyroidism, chronic thyroiditis, hypothyroidism and rarely carcinoma. The most common pathology involved in thyroid hemiagenesis is hyperthyroidism. This report probably represents the first ever reported case of thyroid hemiagenesis from Kuwait.

This 56-year-old Kuwaiti male presented with a left thyroid swelling, a history of progressive fatigue, constipation and weight gain, and exercise intolerance. The patient's preoperative workup included an ultrasound scan, thyroid scan, computed tomography (CT) scan and

thyroid profile. His T4 was 3 pmol/l and TSH was 200 uIU/ml. All investigations revealed a multinodular goiter in the left lobe with an absent right lobe. A fine-needle aspiration biopsy was suspicious for malignancy. The patient underwent left thyroid lobectomy. The operative findings confirmed hemiagenesis of the right lobe and histopathology showed benign multinodular goiter in the left lobe. The parathyroids on the left side were in the normal position.

This case report presents a rare case of hypothyroidism and absent right thyroid lobe. It may help increase awareness of this rare anomaly of the thyroid gland and thus make preoperative diagnosis possible.

KEY WORDS: benign adenoma, carcinoma, goiter, thyroiditis

INTRODUCTION

The common concept of the thyroid gland as a symmetrical structure is not always true. Surgeons have recognized that asymmetry is quite common and the right lobe is usually larger than the left. This fact has also been appreciated by physicians experienced in thyroid scanning. Thyroid hemiagenesis is a rare congenital anomaly in which one lobe of the thyroid fails to develop. The isthmus may or may not be present. Embryologically, the thyroid gland develops as a ventral pocket in the midline in the floor of the pharynx. Abnormal descent of the gland may present as lingual thyroid, thyroglossal cyst, cervical or intrathoracic ectopic and accessory thyroid nodules. Failure of development of one lobe leading to unilateral agenesis is the rarest of all the anomalies. The cause of unilateral agenesis is not known, but a genetic component is possible as suggested by the occurrence of thyroid hemiagenesis among monozygotic twins, and members of the same family^[1]. It is believed that the defect may arise from failure of the original anlage to become bilobed and spread out laterally on both sides.

Agenesis may be total, unilateral, with or without the isthmus. The pattern of descent gives rise to anomalies that are discussed more frequently, such as lingual thyroid, which is reported to occur one in 3,000 births. However, this does not explain the congenital absence of one lobe. In a theory advanced as early as 1949, it is postulated that the unilateral failure of development of the thyroid is related to congenital unilateral absence of thyroid vasculature, but this did not hold true for long, as much contradictory evidence was noted^[2]. Vascular anomalies of the thyroid are common in patients with normal bilobar glands. Absence of the left inferior thyroid artery is seen in five out of 100 cases. Some patients with hemiagenesis of the thyroid have had normal vasculature^[3]. Congenital absence of other paired organs, (*e.g.*, kidneys and lungs) is also more common on left side, again for unknown reasons.

CASE PRESENTATION

A 56-year-old Kuwaiti male was referred for evaluation of a left thyroid mass of four months duration. There was no history of previous radiation to the neck. He gave history of progressive fatigability,

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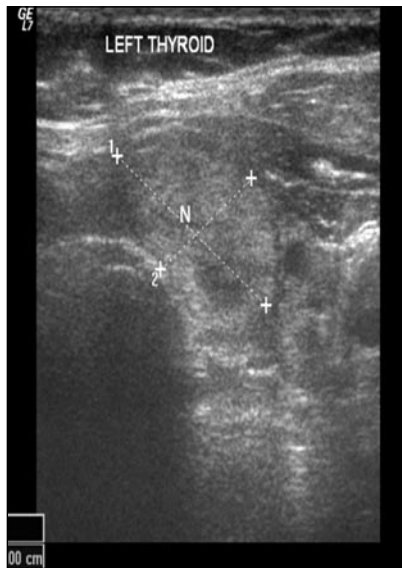


Fig.1 a: Showing US scan of the thyroid left lobe nodule 2 / 3 cm

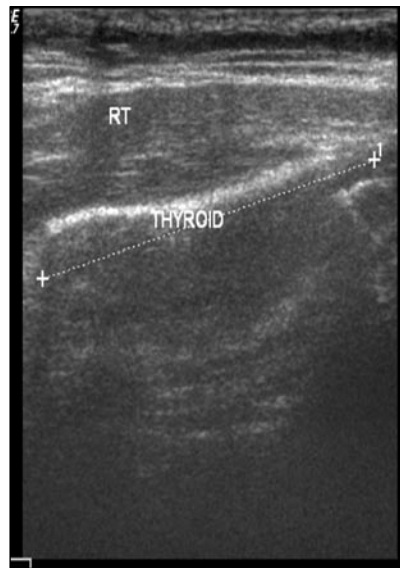


Fig.1 b: Showing US scan of thyroid and the absent right lobe

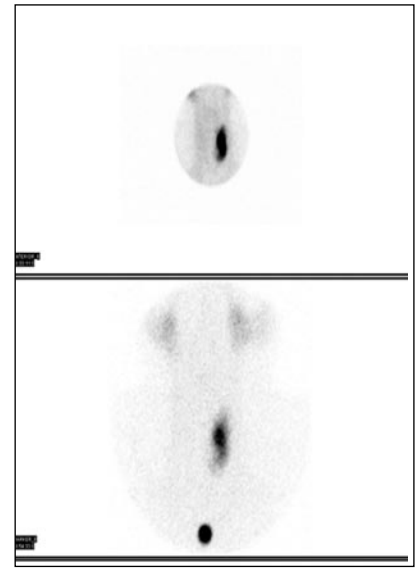


Fig. 2: Thyroid isotope scan showing no uptake on the right side, cold nodule in the lower pole of the left lobe

constipation, exertional dyspnea, weight gain, difficulty in swallowing, and exercise intolerance over the last two years.

His past medical history revealed that he was hypertensive on medical treatment. The patient also gave a strong family history of thyroid disease. His mother and sister had Hashimoto's thyroiditis, his two brothers had multinodular goiter and none of them had thyroid agenesis.

Examination of the patient revealed stable general condition and vital signs. Examination of the neck revealed a left anterior neck swelling that moved with deglutition and no palpable lymph nodes. Complete blood count and biochemistry including calcium and phosphorus were within normal limits. Iodine and parathormone level were not done.

His thyroid function test revealed a TSH of 200 uIU/ml and a T4 of 3 pmol/l suggesting severe hypothyroidism. He was started on thyroxin therapy 100 mcg per day until he became euthyroid within six weeks.

Ultrasound (US) scan of the neck was done before thyroxin therapy (Fig.1a). The left thyroid lobe was enlarged with multiple hyperechoic solid nodules with increased vascularity on color Doppler imaging of the left lobe. Fig. 1b shows an absent right thyroid lobe. Few small bilateral cervical lymph nodes were seen.

Tc99m pertechnetate thyroid scan (Fig. 2) suggested hypofunction of the left lobe with a suspicious cold area on its lower medial aspect. No right lobe was visualized. An US-guided fine needle aspiration done from the cold nodule showed clusters of hyperchromatic follicular cells with a high N / C ratio and irregular nuclear margins suspicious of malignancy.

Computed tomography (CT) scan of the neck (Fig. 3 a & b) was done to delineate the thyroid anatomy and showed a non-visualized right thyroid lobe with prominent heterogeneous left lobe.

Operative findings

The patient underwent neck exploration during which, an absent right thyroid lobe was confirmed and the left thyroid lobe with a nodule at the lower pole was removed with the isthmus and pyramidal lobe. The parathyroid glands were in the normal position.

The patient had an uneventful recovery and was discharged three days after surgery on eltroxin 100 mcg daily. The histopathology report of the left lobe was Hashimoto's thyroiditis and the nodule at the lower pole was reported as nodular hyperplasia without any malignancy.

DISCUSSION

The congenital absence of one lobe of the thyroid is a rare anomaly, seen in fewer than one in 1,000 patients with thyroid disease. In most reported cases there has been a symptomatic, anatomic or functional lesion in the remaining single thyroid lobe. Because of the use of thyroid nuclear scans and US scan for thyroid screening of asymptomatic individuals with a history of neck irradiation, or even normal children, cases of hemiagenesis have been discovered in which there is no other detectable pathology. A review of the available literature shows that patients with thyroid hemiagenesis are predominantly female (ratio 3:1). In addition, the left lobe of the thyroid is absent far more frequently than is the right lobe (ratio 4:1). However, the isthmus is absent in 50% of cases. In our case

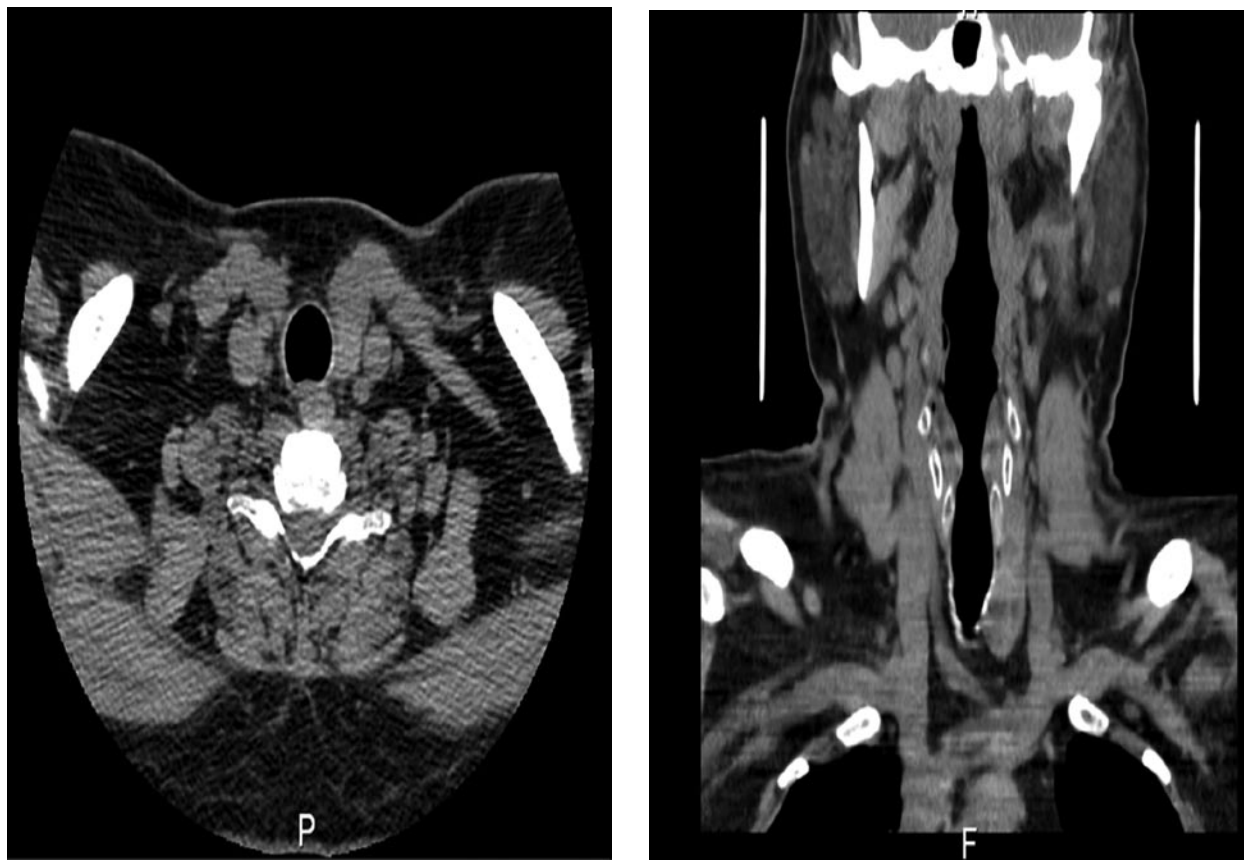


Fig. 3 a & b: Showing CT scan of the neck (sagittal and coronal views) showing prominent left lobe and absent right lobe

the right lobe was absent but the isthmus was there. Thyroid hemiagenesis is associated with diseases in the remaining thyroid lobe which include benign adenoma, multinodular goiter, hyperthyroidism, chronic thyroiditis, hypothyroidism and carcinoma. Some patients were found to be in euthyroid state without any abnormalities. In our case the patient presented with hypothyroidism associated with Hashimoto's thyroiditis. Contrary to our usual practice US scan was done before we received the result of T4 and TSH. High levels of TSH are known to induce several changes in the thyroid and this can mislead the clinician in his management. The total number of cases of thyroid hemiagenesis is uncertain. In a review of literature Milkosch *et al* reported on 256 cases^[4]. The true incidence of thyroid hemiagenesis is difficult to determine since the diagnosis is made in a population being evaluated for some other thyroid pathology. Marshall found one case in 60 autopsies in children^[5]. Harada *et al* found no case in 1,007 necropsies^[6]. Apart from a few sporadic case reports, the majority of cases have been described by Hamburger and Hamburger^[7]. The discovery rate of thyroidal hemiagenesis by imaging has been reported by Maganini and Narendran to be one in 1,700 cases^[8] and by Hamburger and Hamburger to be four in 7,000 thyroid patients^[7]. The prevalence of thyroid hemiagenesis was searched

among normal and healthy children using US scan by Maiorana (0.5%)^[9], Korpál-Szczyrska (0.05%)^[10] and Shabana (0.2%)^[11] and the female predominance and higher incidence of agenesis of the left lobe was confirmed. It would appear that the true frequency can be determined only on the basis of large scale postmortem studies.

The diagnosis of thyroid hemiagenesis depends upon a high index of suspicion when physical examination, thyroid nuclear, US or CT scan reveals no apparent thyroid tissue on one side. Although hemiagenesis of the thyroid is a benign condition, unawareness of its existence may lead to an incorrect diagnosis and the performance of unnecessary surgery with inherent risks. It is possible to diagnose it clinically when one lobe and the isthmus are absent. Two physical signs may be of help. The edge of the trachea is easily palpable and the edge of the sternomastoid muscle on the affected side is much closer to the midline and overlies the trachea instead of being separated from it. The differential diagnosis would include autonomously functioning nodule with suppression of extranodular tissue, unilateral inflammatory diseases (acute or chronic), metastasis from neoplasm elsewhere in the body, or a primary thyroid tumor. A thyroid-releasing hormone (TRH) test will show no uptake in the case of hemiagenesis and

readily demonstrate uptake in the case of suppression of involved lobe in an autonomously functioning nodule. Thyroid scan in a patient with hemiagenesis is quite characteristic and a hockey stick sign may be apparent. The increased functional burden caused by the hemiagenetic gland would promote neoplasia. However, the relevance of this is questionable since all the patients with thyroid hemiagenesis whose TSH levels were measured in Mariani's series had normal TSH value^[2]. Even then it is impossible to avoid the suggestion that long-standing elevated levels that can lead to enlargement of the lobe might have played a role in the development of thyroid carcinoma. Marshall was among the first clinicians to describe numerous anatomic variations of the thyroid, including the clinical entity of hemiagenesis in 1895^[5]. Melnick and Stemkowski described the hockey stick sign by imaging study in patients with thyroid hemiagenesis^[12]. They also reported four patients and reviewed the world literature on the subject of thyroid hemiagenesis which revealed a total of 90 cases; however, only 17 out of these were reported in the American literature^[8]. None of the four patients had thyroid cancer. Sheridan *et al* reported a patient with hemiagenesis and Hashimoto's disease^[13]. The authors identified and preserved the parathyroid glands in normal position on the side of the enlarged thyroid lobe. However, they did not identify the parathyroid on the agenetic side. The information regarding the parathyroid on the agenetic side is not well documented in the literature. Piera *et al* reported three cases of thyroid hemiagenesis in 1986^[14]; however, they documented the normal presence of parathyroid on the side of the enlarged thyroid lobe only in one case. It is important for the thyroid surgeon undertaking surgery on a hemigenetic thyroid to appreciate the position of the parathyroid and to make every effort to preserve the parathyroid on the side of the thyroid lobectomy. McHenry *et al* recently reported seven patients with thyroid hemiagenesis - a collected experience of five physicians^[15]. They reported four female and three male patients ranging in age from 17 to 58 years. The pathologies included follicular adenoma, Graves' disease, and nodular goiter. One patient had follicular carcinoma of the thyroid. They emphasized the need for preoperative recognition of thyroid hemiagenesis in order to make critical decisions regarding surgical intervention. McHenry *et al* suggested that all patients with thyroid hemiagenesis who do not have indications for surgery should have monitoring of their thyrotrophic hormone levels, treatment of thyrotrophic elevation with thyroid hormone, and careful follow-up evaluation for the development of neoplastic disease^[15]. Our case is a unique one compared with cases reported in the literature; the patient was an adult male with absent right thyroid lobe (and not the left which is

more common) with severe hypothyroidism instead of hyperthyroidism (which is more usual).

CONCLUSION

Recognition of this rare congenital anomaly is important to avoid unnecessary contralateral neck exploration with its potential morbidity and also to make sure that patients receive careful follow-up and appropriate therapy when necessary.

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Case Report

Buried Bumper Syndrome

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ABSTRACT

Percutaneous endoscopic gastrostomy is becoming a common and widely accepted procedure for its safety and efficiency. In this case report, we describe a complication, called buried bumper syndrome (BBS) which is becoming more frequent among patients, who have percutaneous endoscopic gastrostomy (PEG) tube inserted. BBS can be serious, even fatal in some cases. We report here, a 42-year-

old lady with suprasellar meningioma who developed BBS, one and half year post-PEG-tube insertion. She started to have abdominal pain and distension, PEG tube blockage and eventually PEG site infection. The PEG tube could not be removed endoscopically and it was removed surgically instead because the PEG tube was buried beneath the gastric mucosa and in the abdominal wall.

KEY WORDS: complication, gastrostomy, migration, PEG

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) was first introduced in 1979 to provide enteral feeding in children and young adult. Currently, PEG feeding is the preferred device recommended by the American Gastroenterological Association (AGA) for providing long-term enteral nutrition for patients, who are not receiving adequate amount of food orally^[1]. It has been more widely used, particularly over the last few years in order to provide long-term nutritional support to patients unable to maintain an adequate oral intake.

As any other procedure, PEG placement has several complications, which can occur during the insertion of the PEG tube or after. There are number of complications that are associated with PEG placement such as aspiration, hemorrhage, peritonitis and gastrocolocutaneous fistula. In this brief article, we focus on a complication of PEG tube called buried bumper syndrome or BBS, which was considered rare earlier, but is becoming more common^[2]. As physicians, we should be aware of this complication that might result in patient's death, if not managed appropriately.

BBS is defined as the migration of the internal bumper of the PEG tube from the gastric lumen and its getting lodged in the gastric wall or anywhere along the gastrostomy tract.

CASE REPORT

A 42-year-old woman was diagnosed with suprasellar meningioma (grade 1) in 2007, which

required craniotomy and total excision of the meningioma. Postoperatively, she developed a stroke that made her dysphasic, blind and affected her swallowing ability. Therefore, PEG tube was placed in Germany.

In Jan 2009, she developed abdominal distension. This was mainly seen during feeding time. She also seemed very uncomfortable during her feed. She had generalized abdominal tenderness. Gastroenterology team was consulted. The initial impression was that the tube was blocked. However, the PEG tube bumper was not seen endoscopically (Fig. 1) and BBS was diagnosed.

Several attempts were made by the gastroenterologist to remove the PEG tube by manual traction as well as by endoscopy. Unfortunately, the tube could not be removed by endoscopy and required surgical removal.

It was decided to re-endoscope the patient to assess the tube status and the presence of BBS. Endoscopy was done in the presence of the surgical team to assess the tube status. Saline was injected during the procedure and it was coming freely into the gastric lumen (Fig. 2). As a result PEG tube feeding was re-started, as suggested by the surgeons.

Unfortunately, the patient developed fever and profuse sweating within 48 hour after feed re-initiation. Pus from PEG tube site was seen. Intravenous antibiotic was started and septic screen was obtained including a swab from the tube site. PEG tube swab culture showed *Staph. aureus* and *Staph. epidermidis*.

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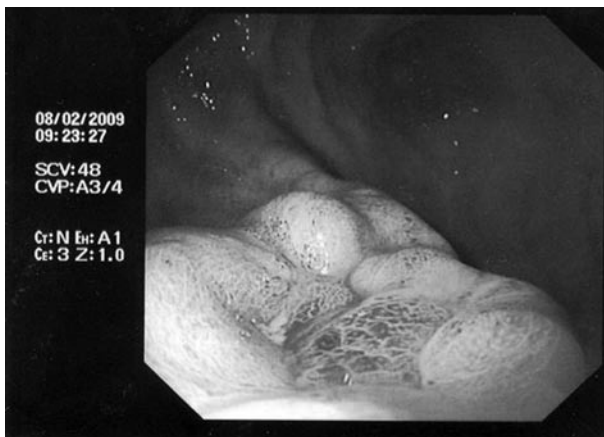


Fig. 1: Showing the gastrostomy opening with the absence of the internal bumper indicating buried bumper syndrome

After a re-evaluation with the gastroenterologist, the surgeons agreed to remove the tube. The tube was removed with no complication.

There was no need to insert another PEG tube as the patient was regaining her ability to swallow and was taking her food orally.

DISCUSSION

The migration of the internal bumper into the gastric mucosa or abdominal wall as complication of PEG tube insertion was first described in 1988^[3]. Later, it was called "Buried Bumper Syndrome" by Klein^[4]. BBS often manifests months to years after PEG tube placement. It presents as abdominal pain mainly during feeding time, difficulty feeding or flushing the tube, and inability to move or rotate the tube because the internal bumper may have been well-buried beneath the gastric mucosa. Nevertheless, BBS has been rarely reported to present as malena resulting in fatal consequences^[5].

BBS is considered as an uncommon complication occurring in 1.6% of patients with PEG replacement^[6]. However, a study from Taiwan suggested that BBS is not that uncommon as previously thought. In addition, it suggested that BBS can occur soon after tube insertion^[2]. This is possibly due to the increasing number of patients with PEG tube.

BBS most commonly is suspected by physical examination. Ultrasound, contrast radiography, computed tomography or magnetic resonance imaging are usually unnecessary in clinical practice. This complication is usually confirmed endoscopically, as in our case.

As physicians with increasing number of patients with PEG tube, it is very important for us to recognize that once BBS is diagnosed, the PEG tube should be removed even if the patient is asymptomatic, because the tube may continue to migrate until it is completely buried in the abdominal wall and that itself may lead to very serious complications such as sepsis, peritonitis, stomach perforation and bleeding.

BBS most likely occurs as a result of excessive tension between the internal and external bumpers leading to gastric ulceration at the bumper site^[7]. Therefore, avoiding external tube traction must be highlighted to the caregivers. For example, avoidance of the placement of gauze pads beneath the external bumper is essential. It has been suggested that amendment of the physical properties of the bumper due to gastric acid exposure can increase pressure necrosis of the gastric wall and results in migration of the bumper^[8]. Also, malnutrition, poor wound healing and significant weight gain secondary to successful enteral nutrition all have been implicated in the incidence of BBS^[9].

Caregivers should be instructed to push in the PEG approximately one centimeter and to rotate it before

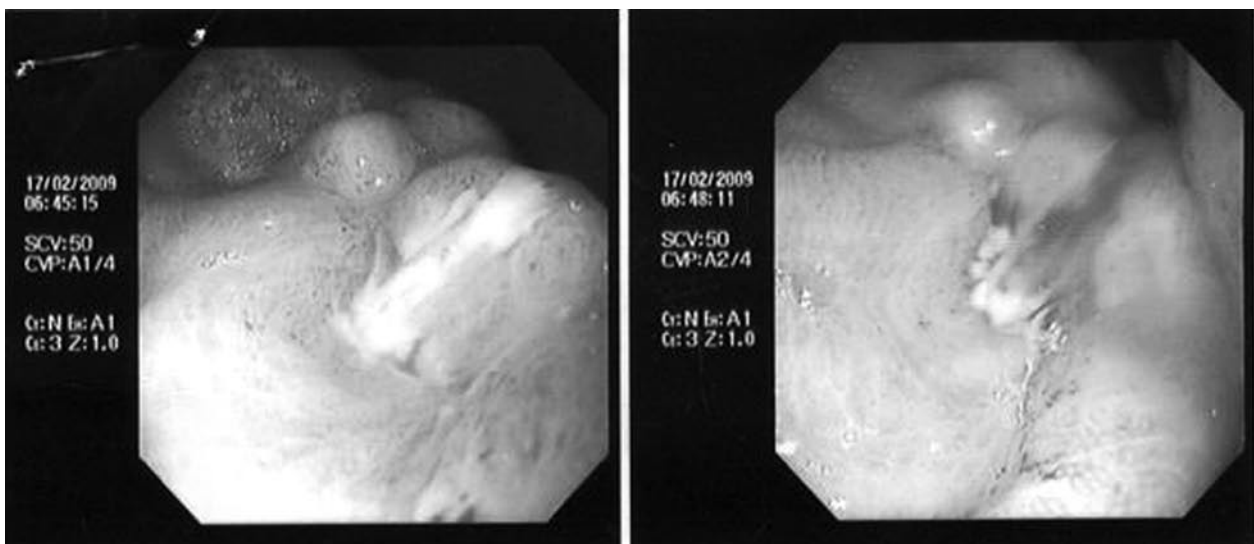


Fig. 2: Showing normal saline coming out of the gastrostomy opening indicating that the tube is patent

positioning the external bumper during daily cleaning. The avoidance of external pulling and traction must be emphasized, as excessive traction can accelerate the development of BBS. Additionally, caregivers must be trained to examine the PEG tube daily for any leakage, tenderness or inability to push in the tube and to consider the possibility of BBS, when any of these signs are present, so that patient can be referred for urgent endoscopy.

The treatment of BBS is varied and a number of techniques have been described in the literature, which were used to manage this syndrome and remove the tube. The simplest one is basically by applying gentle traction force to the tube in order to remove it. Endoscopy is another option, which is commonly used in such cases. However, if the buried tube cannot be removed by manual or endoscopic methods as in our case, or if the patient's condition is complicated by peritonitis or abscess surgical intervention with either laparotomy or laparoscopy approach is needed^[10]. Ultrasound imaging (endoscopic US of the gastric wall with a catheter probe) can provide helpful additional information in deciding whether an endoscopic or surgical approach should be attempted to remove the PEG^[11].

CONCLUSION

Failure to recognize this syndrome may result in serious complications including PEG tube infection, perforation of the stomach, peritonitis, hemorrhage and death. In this case, our patient was lucky and did not develop peritonitis. Physicians should be aware of this serious complication of PEG placement. BBS is not so uncommon and some patients might have recurrent episodes of BBS. The most common presentations are difficulty feeding, peristomal leakage and fixation of the feeding tube. Explicit and specific instructions should be provided to the caregivers to prevent BBS.

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Letter to the Editor

Blount Disease: Bowlegs may not always be a Physiological

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Bowing of the lower extremities is common and is a frequent cause for orthopedic referral^[1]. The role of the physician is to determine if the bowing is physiological or pathological. Among the most common causes of bowlegs are developmental bowing, congenital bowing, tibia vara (Blount disease), neurofibromatosis, osteogenesis imperfecta, rickets, campomelic dysplasia, and achondroplasia^[2].

A 16-month-old girl was referred to our clinic with bowing of legs. She had received Vitamin D prophylaxis and there was no history of trauma or a similar disease in family. Physical examination revealed that her anterior fontanel was closed, and there were no pathological findings in the legs except for bowing. Serum Ca, inorganic phosphate and alkaline phosphatase were normal.

X-ray examination revealed varus deformity of both knee joints in lower extremities. Considering the age of the patient, and the possibility of a physiological bowing, the patient was advised to come for another examination after six months. The patient was brought for the next examination 11 months later. Physical examination revealed that O-bain deformity progressed, while varus deformity of knee joints was apparent, being more prominent in the right knee joint. Inclination towards the medial was apparent on the side of the metaphysis facing the epiphysis and was more prominent on the right. The patient was started on orthosis with a diagnosis of Blount disease.

Tibia vara or Blount disease is an orthopedic problem that may cause growth retardation, believed to result from abnormal stress on the postero-medial proximal tibial physis. Aberrant epiphyseal growth pattern develops due to abnormal stress, which leads to typical varus angulation. The predisposing factors

are listed as starting to walk early, obesity, and being of African-American origin. Early diagnosis and treatment of the disease is critical for prevention of progressive worsening^[1]. The diagnosis is made by antero-posterior radiograph of both legs. Radiography reveals genu varum, abnormal proximal tibia due to depression, irregularity or fracture at the postero-medial metaphysis, and deficiency of the medial epiphysis. While the developmental bowing is typically symmetrical, Blount disease usually develops on one side or asymmetrically. Metaphyseal-diaphyseal angle measurement is significant for both diagnosis and differential diagnosis from developmental bowing. Magnetic resonance imaging is used in Blount disease. Primarily orthosis should be preferred for treatment of children under four years of age and at early stages of the disease. However, at a later stage, tibial and fibular osteotomy is generally done^[3]. As a consequence, early diagnosis and treatment is important in Blount disease, which is a progressive disorder. We believe that pediatric physicians should take Blount disease into consideration when examining cases with childhood bowlegs.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Orthographic Processing and Reading Comprehension among Arabic Speaking Mainstream and LD Children

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Dyslexia 2011; 17:123-142

Two cohorts of mainstream children (grades 2-5) and one cohort of children with learning disabilities (LD; grades 3-5), all Arabic speaking children in Kuwait, were given measures of reading comprehension fluency and orthographic discrimination to assess the relationship between the two. Additional measures of phonological processing (decoding and awareness), speed of processing (rapid naming) and memory (visual as well as phonological / verbal tasks) were included either because these have been found to be predictive of Arabic literacy or to provide an assessment of alternative interpretations of any influence of the orthographic task. The findings indicated that the orthographic measure predicted variability in the comprehension fluency over-and-above that predicted by the other measures in the study. This was significant in the older mainstream children (grades 4 and 5) when controlling for phonological processing, but was not in the younger grades (2 and 3) where experience text that incorporating short vowel markers is dominant. The LD group showed little evidence of an influence of phonological processing but did of orthographic processing. The findings are discussed in terms of the skills required to process Arabic literacy and potential causes of literacy learning difficulties among Arabic children.

A 4-Year Prospective Study of Septicemia in Pediatric Surgical Patients at a Tertiary Care Teaching Hospital in Kuwait

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J Pediatr Surg 2011; 46:679-684

Background: Critically ill children are at high risk for developing nosocomial infections that contributes to death in 4% of all pediatric intensive care unit admissions. This prospective study was undertaken to determine the prevalence of septicemia in the pediatric surgery department of a large tertiary care teaching hospital in Kuwait and to evaluate the risk factors, the microbial etiology, and the antimicrobial susceptibility pattern of the isolated microorganisms.

Methods: All patients admitted to the pediatric surgery department from January 2001 until December 2004 with the diagnosis of septicemia were included in the study, and the microbiologically proven cases were then analyzed. The patients' demographics and risk factors for sepsis were recorded. All positive blood cultures were subjected to identification and antimicrobial susceptibility testing by VITEK 2 (bioMerieux, Marcy l'Etoile, France).

Results: Of 3408 patients suspected to have septicemia, 78 (2.3%) patients developed microbiologically documented septicemias, 26% of those were low-birth weight patients, and 82% were patients with congenital anomalies; 87% of those needed surgical intervention. More than 50% were admitted to the intensive care unit, and 80.5% needed ventilatory support. Fifty-seven percent had early onset septicemia. Gram-positive and gram-negative bacteria accounted for 54% and 39% of the septicemia cases, respectively, whereas *Candida* spp was responsible for 7%. More than 50% of the staphylococci were resistant to cloxacillin, and all gram-positives were uniformly susceptible to glycopeptides and linezolid. Gram-negative bacteria showed variable resistance to cephalosporins (65%), piperacillin/tazobactam (29%), and carbapenems (11%). The attributable mortality rate for these septic episodes was 19% mainly because of gram-negative bacteria and *Candida*.

Conclusion: The main etiologic agents of neonatal septicemia were coagulase-negative *Staphylococcus*, *Pseudomonas aeruginosa*, and members of the family Enterobacteriaceae. Empirical therapy with piperacillin/tazobactam or carbapenems for gram-negative septicemia and glycopeptides for gram-positive septicemia was effective.

First Report of Molecular Detection of Fluoroquinolone Resistance-Associated *GyrA* Mutations in Multidrug-Resistant Clinical *Mycobacterium Tuberculosis* Isolates in Kuwait

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BMC Res Notes 201; 4:123 [Epub ahead of print]

Background: Nearly 5% of all *Mycobacterium tuberculosis* strains worldwide are resistant at least to rifampicin and isoniazid (multidrug-resistant tuberculosis, MDR-TB). Inclusion of a fluoroquinolone and an injectable agent (kanamycin, amikacin or capreomycin) in multidrug therapy is crucial for proper treatment of MDR-TB. The incidence of MDR-TB in Kuwait is ~1%. MDR-TB strains additionally resistant to fluoroquinolones and injectable agents are defined as extensively drug-resistant (XDR-TB) strains and have been detected in >55 countries. Infections with XDR-TB strains have very poor prognosis. This study detected the occurrence of *gyrA* mutations associated with fluoroquinolone resistance among MDR-TB strains in Kuwait.

Findings: Direct DNA sequencing of quinolone resistance-determining region of *gyrA* gene was performed to detect fluoroquinolone resistance-associated mutations in 85 MDR-TB strains isolated from 55 TB patients and 25 pansusceptible *M. tuberculosis* strains. For isolates exhibiting *gyrA* mutations, 3'-end of *rrs* (16S rRNA) was sequenced for the detection of XDR-TB. Fingerprinting of fluoroquinolone resistant MDR-TB strains was performed by detecting mutations in three (81 bp hot-spot, N-terminal and cluster II) regions of *rpoB*, *katG* codon 315 and *inhA*-regulatory region, polymorphisms at *gyrA* codon 95 and *katG* codon 463 by DNA sequencing and by double-repetitive-element PCR for determining strain relatedness. None of the pansusceptible but six of 85 MDR-TB strains contained *gyrA* mutations. Only *gyrA* codon 94 was mutated in all six (D94A in one and D94G in five) strains. Three of six mutant strains were recovered from the same patient while three other strains represented individual patient isolates. Fingerprinting studies identified all individual patient isolates as epidemiologically distinct strains. All six strains with a *gyrA* mutation contained wild-type *rrs* sequence.

Conclusions: Although fluoroquinolones are generally not used for chemotherapy of TB and drug susceptibility testing for second-line drugs is not carried out in Kuwait, four of 55 (7%) individual patient MDR-TB strains contained mutations in *gyrA* gene. The data advocate routine drug susceptibility testing for this important second-line drug for proper management of MDR-TB in Kuwait. Lack of mutations in 3'-end of *rrs* gene that confer resistance to injectable agents reduce the likelihood of occurrence of XDR-TB, at present, in Kuwait.

Symptomatic Secondary Vesical Calculus Formed on an Intrauterine Contraceptive Device Inserted 25 Years Previously

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A 57-year-old postmenopausal woman presented with vague lower abdominal symptoms, dysuria and recurrent urinary tract infection of a year's duration. She had an intrauterine contraceptive device (IUCD) inserted 25 years previously and denied having any significant gynecological or urinary tract symptoms since the device was inserted. CT scan of her pelvis confirmed the presence of an IUCD that had migrated into the urinary bladder and on which a calculus had formed. An attempt at removal of the calculus and IUCD during cystoscopy failed. At cystolithotomy, the IUCD and the calculus were removed intact. IUCDs may produce complications several years after insertion.

Premenstrual Dysphoric Disorder: Prevalence and Effects on Nursing Students' Academic Performance and Clinical Training in Kuwait

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Aims: This study investigated the prevalence of Premenstrual Dysphoric Disorder among non-treatment seeking female students at the College of Nursing Kuwait. It also explored the effects of the disorder on their academic performance as shown by their grade point average and rate of absenteeism at clinical training.

Background: Many women worldwide are unaware of this distressing menstrual disorder which affects about 3 - 8% of women of childbearing age. The cyclical mood symptoms often appear during the last week prior to the onset of menstruation. These symptoms interfere with sufferers activities of daily living including occupational, biopsychosocial and sexual activities.

Design: A prospective observational study

Methods: The study used an adapted Arabic version of Daily Record of Severity of Problem for two menstrual cycles to collect data from 110 nursing students.

Result: Data analysis showed Cronbach's alpha coefficient for the adapted tool was 0.95. The rate of premenstrual dysphoric disorder was 5.6%. Hypotheses tested showed no significant effect on students' academic performance but a significant association with absenteeism at clinical training.

Conclusion: The rate obtained in this study was similar to those from recent studies. Participants with high luteal scores believe that the condition have lowered their quality of life by making them choose to be in isolation during the period.

Relevance to clinical practice: Nursing students' absenteeism rate at clinical training is a predictor of their work absence pattern after qualification. Absenteeism due to premenstrual dysphoric disorder, a cyclic monthly disorder will be of monthly occurrences, if sufferers do not sought medical treatment.

Registered nurses absenteeism will not only result in shortage of trained nursing personnel, but also lowered standard of client care. It also has cost implications as temporary substitute staff may have to be employed during their period of absence or sick leave. This has implications for nursing management.

Emergence of Tigecycline and Colistin Resistance in *Acinetobacter* Species Isolated from Patients in Kuwait Hospitals

Al-Sweih NA, Al-Hubail MA, Rotimi VO

J Chemother 2011; 23:13-16

The development of resistance is a compelling reason for reviewing administration of antibiotics. Recently, most *Acinetobacter* infections are caused by multidrug-resistant (MDR) strains which have necessitated the use of tigecycline or colistin. This study was undertaken to determine the susceptibility of *Acinetobacter* spp. to these and other drugs. A total of 250 *Acinetobacter* isolates were collected from the 8 government hospitals over a period of 6 months. Susceptibility to 18 antibiotics, including tigecycline and colistin, was investigated by determining their minimum inhibitory concentrations using E test. Of the 250 isolates, 13.6% and 12% were resistant to tigecycline and colistin. A total of 25.2% and 37.2% were resistant to imipenem and meropenem, respectively. Of the 250 isolates 88.4% were MDR. This relatively high prevalence of tigecycline and colistin-resistant isolates indicates an emerging therapeutic problem which may severely compromise the treatment of MDR *Acinetobacter* spp. infections in Kuwait.

Knowledge and Attitudes About HIV/AIDS of Dental Students from Kuwait and Sri Lanka

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J Dent Educ 2011; 75:574-581

Several studies regarding knowledge and attitudes of dental students towards HIV/AIDS have been reported from various countries. However, to the best of our knowledge, an international comparison between countries with diverse cultural and educational backgrounds has not been reported in the literature. The aim of this study was to compare the knowledge and attitudes towards HIV/AIDS of dental students of Kuwait University (KU), Kuwait and the University of Peradeniya (UP), Sri Lanka, the only dental schools in the respective countries. A cross-sectional survey was conducted among a total of 258 dental students, representing the clinical years of both universities, using a similar structured questionnaire with sixty questions to examine their knowledge of various aspects of HIV/AIDS and thirteen questions to examine their attitudes towards the disease. The mean knowledge and attitude scores were calculated and compared between students from the two universities using t-test with SPSS 17.0. A total of 215 questionnaires were completed and returned, giving a total response rate of 83.3 percent. The KU students were significantly more knowledgeable ($p = 0.018$) regarding HIV/AIDS than the UP students. However, the UP students demonstrated a more highly significant positive attitude ($p < 0.001$) towards the disease than those in KU. This information might help to define strategies to improve the quality of education in these countries.

Prevalence of Human Papillomavirus among Women with Normal Cervical Cytology in Kuwait

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This study was undertaken to determine the prevalence and type specific distribution of human papillomavirus (HPV) in women with normal cervical cytology in Kuwait. The study is the first of its type in Kuwait and one of few in the Middle East. The age specific distribution of HPV types was determined in 3,011 ThinPrep samples taken from women seeking routine gynaecological care. ThinPrep samples were screened for HPV DNA by real-time PCR. The type specific distribution of the viruses was determined by PCR-based sequencing. The results showed that HPV DNA was detected in 71 women (2.4%), and 21 different HPV genotypes were detected, comprising eight high-risk (HR) (16, 31, 33, 53, 56, 58, 66, and 73), seven low-risk (LR) (6, 11, 54, 61, 70, 81, and 90), four intermediate-risk (IR) (67, 82, 83, and 84) and HPV 102 and HPV 106. LR HPV types were found in 71.8% of infected samples, HR types in 32.3%, and IR types in 7%. With regard to age, 40.8% of all HPVs were found in women 30 - 39 years of age, 29.6% in women 40 - 49 years of age, 19.7% in women over 50 years and 9.9% in women less than 34 years old. The study shows that the prevalence of HPV infection in Kuwait is among the lowest in the world and suggests that HPV vaccine could prevent the development of HPV associated cervical cancer in 1.39% of young females living in Kuwait. However, more extensive population-based studies should be undertaken before implementing HPV vaccination.

Cerebral venous Thrombosis in Kuwait. Clinical Presentation, Risk Factors, and Management

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Neurosciences (Riyadh) 2011; 16:129-316

Objective: To explore the pattern of clinical presentations, risk factors, and the sinuses involved in cases of cerebral venous thrombosis (CVT) treated in a tertiary neurological center in Kuwait.

Methods: A retrospective analysis of cases of CVT treated at Ibn Sina Hospital, Kuwait, from January 2000 to October 2010. The records of 71 patients were retrieved and entered in a database. All patients were evaluated with hypercoagulable work up and relevant neuro-imaging studies.

Results: Seventy-one patients were included in our study, with a male to female ratio of 1:1.5. The clinical presentations were: headache (93%), seizures (31%), and focal neurological signs (37%). Over two-thirds (n = 30) of female patients had a history of oral contraceptive use. Papilledema with raised intracranial pressure was recorded in 20 patients (28%), ovarian hyper-stimulation syndrome with CVT in one patient, and possible Neuro-Behcet's in 10% (n = 7). The venous sinuses involved were superior sagittal sinus in 59% (n = 42), and transverse and straight sinuses in 54% (n = 38). Hemorrhagic venous infarctions were seen in 18% (n = 13). Fifty percent of patients recovered within 2 - 4 weeks, 15 patients (21%) recovered within 4 -12 weeks, and 15 patients (21%) required intensive care unit care with ventilator support for 1 - 2 weeks.

Conclusion: Oral contraceptive use was the primary risk factor in female patients. Early diagnosis and immediate treatment with anticoagulants reduce the morbidity and mortality. Serum D-dimer level is more helpful for early diagnosis with sensitivity of 58%.

Forthcoming Conferences and Meetings

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Babichan K Chandy

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Email: espid@kenes.com

Website: <http://www.kenes.com/espid>

4th National Conference: **Addiction and the Liver** 2011

Jun 8 - 9, 2011

Hallam Conference Centre, London, *United Kingdom*

Contact: Florence Doel, St Judes Church, Dulwich Road,
Herne Hill, London SE24 0PB

Telephone: +44 (0) 207 501 6762;

Fax: +44 (0) 207 978 8319

Email: flo.doel@markallengroup.com;

Website: http://www.mahealthcareevents.co.uk/cgi-bin/go.pl/conferences/detail.html?conference_uid=230

Hot Topics in **Neurology and Neurosurgery** for the Primary Clinician

Jun 9 - 10, 2011

Siebens Medical Education Building, Mayo Clinic,
Rochester, MN, *United States*

Contact: Mayo School of Continuous Professional
Development, 200 1st St. SW; Plummer 2-60, Rochester,
MN

Telephone: 1-800-323-2688; Fax: 507-284-0532

Email: cme@mayo.edu Website: <http://www.mayo.edu/cme/neurology-and-neurologic-surgery>

1st Joint Congress for **Gynecology, Obstetrics and Fertility**

Jun 10 - 12, 2011

InterContinental Warsaw, Warsaw, *Poland*

Contact: Shirley Dinenson, 18 Avenue Louis-Casai, 1209
Geneva, Switzerland

Telephone: +41 22 5330 948; Fax: +41 22 5802 953

Email: sdinenson@paragon-conventions.com

Website: <http://www.gofip.net/>

20th World Congress for **Sexual Health**

Jun 12 - 16, 2011

SECC – Scottish Exhibition and Conference Centre,
Glasgow, *United Kingdom*

Contact: Secretariat, 1-3 Rue de Chantepoulet, CH-1211
Geneva 1, Switzerland

Telephone: +41 22 908 0488; Fax: +41 22 906 9140

Email: was@kenes.com

Website: <http://www.kenes.com/was>

Advances in **Breast, Endocrine, and Cancer Surgery**

Jun 16 - 18, 2011

Radisson University Hotel, Minneapolis, MN, *United States*

Contact: Bonnie Boucher, 420 Delaware St SE,
Minneapolis, MN55414

Telephone: 612-626-1999

Email: dos@umn.edu; Website: <http://www.cme.umn.edu>

Laryngology 2011

Jun 20 - 22, 2011
 The Royal College of Surgeons of England, London,
United Kingdom
 Contact: Secretariat, 1st Floor, Chesterfield House, 385
 Euston Road, NW1 3AU
 Telephone: +44 (0) 207 383 8030
 Email: laryngology2011@gmail.com; Website: <http://www.kenes.com/laryngology>

Family Medicine: A Review and Update of Common Clinical Problems

Jun 20 - 24, 2011
 Sarasota, FL, *United States*
 Contact: Christy or Kathryn
 Telephone: 1-866-267-4263 or 1-941-388-1766
 Fax: 1-941-365-7073
 E-Mail: mail@ams4cme.com

6th National Neuroscience Conference: Epilepsy of Children

Jun 23, 2011
 The Hallam Conference Centre, London, *United Kingdom*
 Contact: Florence Doel, St Judes Church, Dulwich Road, Herne Hill, London SE24 0PB
 Telephone: +44 (0) 207 501 6762
 Fax: +44 (0) 207 978 8319
 Email: flo.doel@markallengroup.com
 Website: http://www.mahealthcareevents.co.uk/cgi-bin/go.pl/conferences/detail.html?conference_uid=234

34th Annual Occupational Safety and Health Summer Institute

Jul 25 - 29, 2011
 Norfolk, Virginia, *United States*
 Contact: NC ERC, PO Box 126248
 Telephone: 919-962-2101 Fax: 919-966-7579
 Email: osherc@unc.edu; Website: <http://osherc.sph.unc.edu/>

6th International Pediatric Transplant Association (IPTA) Congress on Pediatric Transplantation

Jun 25 - 28, 2011
 Montreal, QC, *Canada*
 Contact: Congress Secretariat
 Telephone: 856-439-0500 ext. 4496 Fax: 856-439-0525
 E-Mail: bbilofsky@ahint.com or info@IPTAonline.or

Summer Radiology Symposium at The Sagamore

Jun 27 - Jul 1, 2011
 The Sagamore, Lake George, NY, *United States*
 Contact: Marisa, 462 First Avenue, New York, NY 10016
 Telephone: 2122630724
 Email: marisa.bruno@nyumc.org
 Website: <http://www.radcme.med.nyu.edu>

Dermatology for Primary Care

Jun 27 - Jul 1, 2011
 Hyatt Regency, Sarasota, FL, *United States*
 Contact: D. Reece Pierce, PA-C, P.O. Box 49947, Sarasota, FL 34230-6947
 Telephone: 1-866-267-4263; Fax: 941-365-7073
 Email: mail@ams4cme.com
 Website: <http://www.ams4cme.com>

14th World Conference on Lung Cancer

Jul 03 - 07, 2011
 Amsterdam, *Netherlands*
 Contact: Grit Schoenherr
 Telephone: 1-604-681-2153; Fax: 1-604-681-1049
 E-Mail: wclc2011-marketing@icsevents.com

2011 Plastic Surgery Congress

Jul 6 - 10, 2011
 Gold Coast Convention and Exhibition Centre
 The Gold Coast, *Australia*
 Contact: Congress Secretariat, Suite 503, L5 Christie Street, St Leonards, NSW
 Telephone: +61 2 9431 8699
 Email: 2011psc@conferenceaction.com.au
 Website: <http://www.plasticsurgerycongress.org.au/>

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
 Telephone: 41-0-22-7-100-800; Fax: 41-0-22-7-100-899
 E-Mail: info@iasociety.org

General Pediatrics Update

Jul 18 - 21, 2011
 The Sea Pines Resort, Hilton Head Island
 SC, *United States*
 Contact: Catherine Burrison, 32 Greenwood Drive, HHI, SC, 29928
 Telephone: 1-800-335-2582
 Email: cburrison@seapines.com
 Website: <http://www.seapinescme.com>

Recent advances in Dermatology and Internal Medicine

Jul 23 - Aug 10, 2011
 The Arctic, *Greenland*
 Contact: Dr D Czarnecki
 Telephone: 613-9887-0066
 Fax: 613-9887-0044
 E-Mail: dbczarnecki@gmail.com

Internal Medicine Update

Jul 25 - 28, 2011
 The Sea Pines Resort, Hilton Head Island,
 SC, *United States*
 Contact: Catherine Burrison, 32 Greenwood Drive, HHI, SC, 29928
 Telephone: 1-800-335-2582
 Email: cburrison@seapines.com; Website: <http://www.seapinescme.com>

Managing Coding & Reimbursement Challenges in **Neurosurgery**

Jul 28 - 29, 2011

Hilton Boston Back Bay, Boston, MA, *United States*

Contact: Heather Hodge, 5550 Meadowbrook Dr, Rolling Meadows, IL 60008

Telephone: 847-378-0500; Fax: 847-378-0600

Email: epm@aans.org; Website: <http://www.aans.org/~Media/Files/Education%20and%20Meetingf/Education%20Courses/2011CodingCourseLis>

35th Annual Meeting of the Christian **Ophthalmology** Society

Jul 28 - 31, 2011

The Homestead, Hot Springs, VA, *United States*

Type of Event: Conference

Contact: Lee Helms, M.D., 728 S. Atlantic Avenue, Virginia Beach, VA, 23451

Telephone: 504-839-1766

Email: annualmeeting@cosw.org

Website: <http://www.cosw.org>

Neurosurgeon as CEO The Business of **Neurosurgery**

Jul 30 - 31, 2011

Hilton Boston Back Bay, Boston, MA, *United States*

Contact: Heather Hodge, 5550 Meadowbrook Dr., Rolling Meadows, IL 60008

Telephone: 847-378-0500 Fax: 847-378-0600

Email: epm@aans.org; Website: <http://www.AANS.org>

NYU **Clinical Imaging** Symposium in Santa Fe

Aug 1 - 5, 2011

La Posada, Santa Fe, NM, *United States*

Contact: Marisa, 462 First Avenue, New York, NY 10016

Telephone: 2122630724

Email: marisa.bruno@nyumc.org; Website: <http://www.radcme.med.nyu.edu>

2011 summer (Academy) Meeting of the American Academy of **Dermatology**

Aug 03 - 07, 2011

New York, NY, *United States*

Contact: American Academy of Dermatology

Telephone: 866-503-SKIN (7546) / 847-240-1280; Fax: 847-240-1859

E-Mail: MRC@aad.org

Mayo Clinic **Cardiology** Update 2011

Aug 5 - 7, 2011

Enchantment Resort, Sedona, AZ, *United States*

Contact: Staci King, 13400 E. Shea Boulevard, Scottsdale, AZ 85259

Telephone: (480) 301-4580

Email: king.staci@mayo.edu Website: <http://www.mayoclinic.org/arizona/>

Targeted **Antibodies for Cancer** 2011

Aug 10 - 11, 2011

Etc. Venues Paddington, London, *United Kingdom*

Contact: Florence Doel, St Judes Church, Dulwich Road, Herne Hill, London SE24 0PB

Telephone: +44 (0) 207 501 6762

Fax: +44 (0) 207 978 8319

Email: flo.doel@markallengroup.com

Website: http://www.mahealthcarevents.co.uk/cgibin/go.pl/conferences/detail.html?conference_uid=248

10th Asia Pacific Congress of **Endoscopic Surgery**

Aug 11 - 13, 2011

Suntec Singapore, Singapore, *Singapore*

Contact: Stella Chee, 2 Leng Kee Road #04-01 Thye Hong Centre Singapore 159086

Telephone: 6563795259; Fax: 6564752077

Email: admin@elsa2011singapore.com; Website: <http://www.elsa2011singapore.com>

Rhinofest 2011: Mayo Clinic Comprehensive Course in **Rhinology**

Aug 18 - 21, 2011

Siebens Medical Education Building,

Rochester, MN, *United States*

Contact: MSCPD, 200 1st St. SW, Plummer 2-60, Rochester, MN 55905

Telephone: 1-800-323-2688; Fax: 507-284-0532

Email: cme@mayo.edu; Website: <http://www.mayo.edu/cme/rhinofest-2011R080>

2011 **Infectious Disease** Board Review Course

Aug 27-31, 2011

Ritz-Carlton, Tysons Corner, McLean, VA, *United States*

Contact: Julie Vastyan, 2300 I Street, NW, Ross Hall, Suite 313D, Washington, DC 20037

Telephone: 800-314-1423

Email: julie.vastyan@gwumc.edu; Website: <http://www.IDBoardReview.com>

23rd European Congress of **Pathology**

Aug 27 - Sep 01, 2011

Helsinki, *Finland*

Contact: Prof. Veli Peka Lehto

Telephone: 358-9-191-26412; Fax: 358-9-191-26700

E-Mail: veli-pekka.lehto@helsinki

6th World Congress on **Itch**

Sep 4 - 6, 2011

Oceanopolis, Brest, France

Contact: Pr Laurent Misery, Brest University Hospital, 24 Rue Chauchat, 75009 Paris

Telephone: + 33 298 22 33 15; Fax: + 33 298 22 33 82

Email: registration@itchbrest.com

Website: <http://www.itchbrest.com>

World Endometriosis Society 11th World Congress on
Endometriosis
Sep 04 - 07, 2011
Montpellier, *France*
Contact: Congress Secretariat
Phone: 33-467-619-414; Fax: 33-467-634-395
E-Mail: mail@ams.fr

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
Telephone: 630-574-0220; Fax: 630-574-0661

International Congress on Controversies in **Stem Cell Transplantation and Cellular Therapies** (COSTEM)
Sep 8 - 11, 2011
Berlin, *Germany*
Contact: Organizing Secretariat, 53 Rothschild Boulevard, 61000, Tel Aviv, Israel
Telephone: 97235666166; Fax: 97235666177
Email: costem@comtecmed.com
Website: <http://www.comtecmed.com/costem>

30th Annual ESRA Congress - European Society of Regional **Anaesthesia & Pain Therapy**
Sep 7 - 10, 2011
Maritim Hotel & Internationales Congress Center Dresden, Dresden, *Germany*
Contact: Kenes International, 1-3, Rue de Chantepoulet, Geneva CH-1211, Switzerland
Telephone: +41 22 908 0488
Email: esra-congress@kenes.com; Website: <http://www.kenes.com/esra2011>

15th Congress of the European Federation of **Neurological Societies**
Sep 10 - 13, 2011
Budapest Hungexpo, Budapest, *Germany*
Contact: Secretariat, 1-3 rue de Chantepoulet, 1211 Geneva 1, Switzerland
Telephone: +41 22 908 04 88; Fax: +41 22 732 28 50
Email: efns2011@kenes.com; Website: <http://www.efns.org/efns2011>

17th International Meeting of the European Society of **Gynaecological Oncology**
Sep 11 - 14, 2011
Milan Convention Center (MIC), Milano, *Italy*
Contact: Secretariat, 1-3 rue de Chantepoulet, CH-1211 Geneva, Switzerland
Telephone: +41 22 908 0488; Fax: +41 22 906 9140
Email: laryngology@gmail.com; Website: <http://www.kenes.com/esgo>

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

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

43rd International Danube **Neurology** Symposium 2011
Oct 6 - 8, 2011
Technical University of Dresden, Dresden, *Germany*
Contact: Vanessa Jansen, Zum Ehrenhain 34, 22885 Barsbüttel
Telephone: 0406708820
Email: danube2011@cpo-hanser.de
Website: <http://www.danube2011.org/welcome.html>

Transplant Immunosuppression 2011: The Difficult Issues
Oct 12 - 15, 2011
Radisson University Hotel, Minneapolis MN, *United States*
Contact: Office of Continuing Medical Education, University Park Plaza Suite 601; 2829 University Ave SE; Minneapolis, MN 55414
Telephone: 612-626-7600 or 800-776-8636
Fax: 612-626-7766
Email: cme@umn.edu
Website: <http://www.cmecourses.umn.edu>

ASA 2012: American Society of **Anesthesiologists** Annual Meeting
Oct 13 - 17, 2012
Washington, DC, *United States*
Contact: Meeting Organiser
E-Mail: annmtg@asahq.org

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

Clinical State of the Art: **Body MRI**
Oct 17 - 18, 2011
NYU Langone Medical Center, New York, NY, *United States*
Contact: Marisa, 462 First Avenue, New York, NY 10016
Telephone: 2122630724
Email: marisa.bruno@nyumc.org; Website: <http://www.radcme.med.nyu.edu>

7th International Congress on Vascular Dementia

Oct 20 - 23, 2011

Revel Hotel Riga, Riga, *Latvia*

Contact: Secretariat, 1-3, rue de Chantepoulet,

CH-1211 Geneva 1

Telephone: +41 22 908 0488; Fax: +41 22 906 9140

Email: vascular@kenes.com; Website: <http://www.kenes.com/vascular>**2011 Advances in Inflammatory Bowel Diseases**

Oct 21 - 23, 2011

Hollywood, FL, *United States*

Contact: Theresa Jones

Telephone: 678-242-0906; Fax: 678-242-0920

E-Mail: meetings@imedex.com

The Canadian Cardiovascular Congress 2011

Oct 21 - 26, 2011

Vancouver, BC, *Canada*

Contact: Jacqueline Lane

Telephone: 613-569-3407 ext 404; Fax: 613-569-6574

E-Mail: lane@ccs.ca

2011 Annual Meeting of the American Academy of Ophthalmology

Oct 22 - 25, 2011

Orlando, FL, *United States*

Contact: American Academy of Ophthalmology

Telephone: 415-447-0320

E-Mail: meetings@aao.org

9th International Congress on Coronary Artery Disease from Prevention to Intervention

Oct 23 - 26, 2011

Hilton Molino Stucky, Venice, *Italy*

Contact: Secretariat, 1-3 rue de Chantepoulet, Geneva CH-1211, Switzerland

Telephone: +41 22 908 0488; Fax: +41 22 906 9140

Email: coronary@kenes.com; Website: <http://www.kenes.com/iccad>**American College of Surgeons 97th Annual Meeting**

Oct 23 - 27, 2011

San Francisco, CA, *United States*

Contact: American College of Surgeons

Telephone: 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

Telephone: 703-998-8890; Fax: 703-998-8893

E-Mail: thyroid@thyroid.org

Internal Medicine | Istanbul to Luxor cruise

Oct 29 - Nov 12, 2011

Istanbul, *Turkey*

Contact: Sea Courses Cruises

Phone: 1-888-647-7327; Fax: 1-888-547-7337

E-Mail: cruises@seacourses.com

20th International Conference on Oral and Maxillofacial Surgery

Nov 1 - 4, 2011

Casa Piedra, Santiago, *Chile*

Contact: Secretariat, La Concepción 266 Office 501, Santiago, Chile

Telephone: +56 2 946 2633; Fax: +56-2 946 2643

Email: icoms2011@kenes.com; Website: <http://www.icoms2011.com>**WINFOCUS 2011: 7th World Congress on Ultrasound in Emergency & Critical Care Medicine**

Nov 02 - 06, 2011

New Delhi, *India*

Contact: Winfocus Secretariat

Telephone: 39-051-230-385; Fax: 39-051-221-894

E-Mail: secretariat@winfocus.org

ASN Renal Week 2011

Nov 08 - 13, 2011

Philadelphia, PA, *United Kingdom*

Contact: The American Society of Nephrology, 1725 I Street, NW, Suite 510, Washington, DC 20006 Phone: 202-659-0599; Fax: 202-659-0709

E-Mail: email@asn-online.org

Sepsis Congress 2011

Nov 12 - 13, 2011

The Leela Kempinski hotel, New Delhi, *India*

Contact: Dr O Singh/ Dr Y Javeri, Department of Critical Care Medicine, Max Super Specialty Hospital 1, Press Enclave Road, Saket, New Delhi, India 110017

Telephone: +91-9999261685

Email: sepsis.congress@gmail.com; Website: <http://www.apcc-india.com>**XXth World Congress of Neurology**

Nov 12 - 17, 2011

Palais des Congrès de la Palmeraie, Marrakesh, Morocco

Contact: Secretariat, 1-3 Rue de Chantepoulet, CH-1211 Geneva 1

Telephone: +41 22 908 0488; Fax: +41 22 906 9140

Email: wcn@kenes.com Website: <http://www.kenes.com/wcn>

7th World Congress of the World Society for **Pediatric Infectious Diseases**

Nov 16 - 19, 2011

Melbourne Convention Exhibition Centre

Melbourne, *Australia*

Contact: Secretariat, 1-3, rue de Chantepoulet, Geneva 1

Telephone: +41 22 908 0488; Fax: +41 22 906 9140

Email: wspid@kenes.com

Website: <http://www.kenes.com/wspid>

Laboratory **Diagnosis of Fungal Infections: The Last Course**

Nov 16 - 18, 2011

Kahler Grand Hotel, Rochester, MN, *United States*

Contact: Kay Kenitz, 3050 Superior Drive NW, Rochester, Minnesota 55901

Telephone: 800-533-1710

Email: kenitz.mary@mayo.edu

Website: <http://www.mayomedicallaboratories.com/education/mycology/index.html>

5th **Autoimmunity** Congress Asia

Nov 17 - 19, 2011

Suntec Singapore, *Singapore*

Contact: Secretariat, 1-3, Rue de Chantepoulet, CH-1211 Geneva 1

Telephone: +41 22 908 0488; Fax: +41 22 906 9140

Email: aca@kenes.com

Website: <http://www.kenes.com/aca>

14th World Congress on Controversies in **Obstetrics, Gynecology & Infertility** (COGITM)

Nov 17 - 20, 2011

Le Meridien Montparnasse, Paris, *France*

Contact: Ruthi Yahav, 10 quai Charles de Gaulle, Lyon 69463, France

Telephone: 33 4 78 176 176; Fax: 33 4 78 176 257

Email: cogi@congressmed.com; Website: <http://www.congressmed.com/cogi>

Website: <http://www.congressmed.com/cogi>

14th World Congress on Controversies in **Obstetrics, Gynecology & Infertility** (COGITM)

Nov 17 - 20, 2011

Le Meridien Montparnasse, Paris, *France*

Contact: Ruthi Yahav, 10 quai Charles de Gaulle, Lyon 69463, France

Telephone: 33 4 78 176 176; Fax: 33 4 78 176 257

Email: cogi@congressmed.com; Website: <http://www.congressmed.com/cogi>

Website: <http://www.congressmed.com/cogi>

Breast Cancer Controversies 2011

Nov 29 - 30, 2011

The Royal College of Physician, London, *United Kingdom*

Contact: Secretariat, Chesterfield House, 385 Euston Road, London NW1 3AU

Telephone: +44 (0) 207 383 8030; Fax: +44 (0) 207 7838 8040

Email: breastscreening@kenes.com

Website: <http://www.breastcancermeeting.co.uk>

Website: <http://www.breastcancermeeting.co.uk>

Website: <http://www.breastcancermeeting.co.uk>

Website: <http://www.breastcancermeeting.co.uk>

AANS/CNS Section on **Pediatric Neurological Surgery**

Nov 29 - Dec 2, 2011

Hilton Austin, Austin, TX, *United States*

Contact: Jennifer Healy, 5550 Meadowbrook Dr., Rolling Meadows, IL 60008

Telephone: 847-378-0500 Fax: 847-378-0600

Email: meetings@aans.org

Website: <http://http://www.AANS.org>

Website: <http://http://www.AANS.org>

Website: <http://http://www.AANS.org>

AORTIC 2011 - Entering the 21st Century for **Cancer Control** in Africa

Nov 30 - Dec 03, 2011

Cairo, Egypt

Contact: Belmira Rodrigues

Telephone: 27-21-532-6333

Fax: 27-21-532-6331

E-Mail: aortic2011@globalconf.co.za

The 4th International Conference on FIXED combination, in the treatment of **Hypertension, Dyslipidemia and Diabetes**

Dec 1 - 4, 2011

Marriott Rive Gauche Hotel, Paris, *France*

Contact: Ms. Ravit Levy, 18 Avenue Louis-Casai, 1209 Geneva, Switzerland

Telephone: +41 22 5330 948; Fax: +41 22 5802 953

Email: rlevy@paragon-conventions.com

Website: <http://www.fixedcombination.com/2011>

Website: <http://www.fixedcombination.com/2011>

XIX WFN World Congress on **Parkinson's Disease and Other Movement Disorders**

Dec 11 - 14, 2011

Shanghai International Convention Center

Shanghai, *China*

Contact: Secretariat, 1-3 Rue de Chantepoulet, CH-1211, Geneva 1

Telephone: + 41 22 908 0488; Fax: + 41 22 906 9140

Email: parkinson2011@kenes.com; Website: <http://www2.kenes.com/parkinson/Pages/Home.aspx>

Website: <http://www2.kenes.com/parkinson/Pages/Home.aspx>

Website: <http://www2.kenes.com/parkinson/Pages/Home.aspx>

World Congress on Debates and Consensus in **Bone, Muscle and Joint Diseases (BMJD)**

Jan 19 - 22, 2012

CCIB, Barcelona, *Spain*

Contact: Project Manager, Tel Aviv, 69463 Lyon Cedex 06 France

Telephone: +33 4 78 176 176

Email: bmjd@congressmed.com; Website: <http://www.congressmed.com/bmjd>

Website: <http://www.congressmed.com/bmjd>

Website: <http://www.congressmed.com/bmjd>

Website: <http://www.congressmed.com/bmjd>

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Website: <http://www.congressmed.com/bmjd>

Website: <http://www.congressmed.com/bmjd>

Website: <http://www.congressmed.com/bmjd>

15th World Conference on **Tobacco or Health**

Mar 21 - 24, 2012

Singapore, *Singapore*

Contact: Su-Ying Low, Department of Respiratory and Critical Care Medicine

Telephone: +65 63214700; Fax: +65 62271736

Email: low.su.ying@sgh.com.sg; Website: <http://wctoh2012.org/>

Website: <http://wctoh2012.org/>

Website: <http://wctoh2012.org/>

Website: <http://wctoh2012.org/>

Website: <http://wctoh2012.org/>

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Website: <http://wctoh2012.org/>

Website: <http://wctoh2012.org/>

Website: <http://wctoh2012.org/>

Website: <http://wctoh2012.org/>

15th World Congress of **Anesthesiologists** (WCA) 2012

Mar 25 - 30, 2012

Buenos Aires, *Argentina*

Contact: Janet McCready

Telephone: 44-0-1462-438-409; Fax: 44-0-1462-452-562

E-Mail: janet.mccready@choicelive.com

Website: <http://www.choicelive.com>

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Website: <http://www.choicelive.com>

Website: <http://www.choicelive.com>

Website: <http://www.choicelive.com>

Aseptic Surgery Forum 2012

Mar 29 - 30, 2012

Cité des Sciences, PARIS, *France*

Sponsoring Organization: Oriex Communication

Contact: sylviane ROBINET, 25 Rue André Joineau - 93310 Le Pré Saint Gervais

Telephone: +33 1 48 91 89 89; Fax: 0033148434994

Email: s.robinet@simpleway.fr; Website: <http://www.aseptic-surgery-forum.com>**American Association for Thoracic Surgery (AATS) 92nd Annual Meeting 2012**

Apr 28 - May 02, 2012

San Francisco, CA, *United States*

Contact: Meeting Organiser: American Association for Thoracic Surgery (AATS)

Telephone: 978-927-8330; Fax: 978-524-8890

12th International Conference on Cochlear Implants and other Implantable Auditory Technologies

May 3 - 5, 2012

Baltimore, MD, *United States*

Sponsoring Organization: Johns Hopkins University (JHU)

Contact: Corinne Aderhold, 1101 North Delaware, Suite 200, Indianapolis, IN 46202

Telephone: 1-317-635-4755; Fax: 1-317-635-4757

Email: corinne@cmcglobal.com Website: <http://ci-2012.com/>**Immunology 2012: 99th Annual Meeting of the American Association of Immunologists**

May 04 - 08, 2012

Boston, MA, *United States*

Contact: Meeting Organiser: The American Association of Immunologists

Telephone: 301-634-7178; Fax: 301-634-7887

E-Mail: meetings@aai.org**CINP 2012 - Congress of the International College Neuropsychopharmacology**

Jun 3 - 7, 2012

Stockholm, *Sweden*

Contact: Vivien Kitzing, Paulsborner Str. 44, Glasgow G74 3XH, Scotland UK

Telephone: +49 30 300 669 0

Email: vkitzing@cpo-hanser.de; Website: <http://www.cinp2012.com>**12th Congress of the European Society of Contraception and Reproductive Health**

Jun 20 - 23, 2012

Athens, *Greece*

Contact: Nancy Habils

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E-Mail: congress@contraception-esc.com**15th World Congress of Pain Clinicians**

Jun 27 - 30, 2012

Granada Convention Center, Granada, *Spain*

Contact: Kenes International, 1-3 Rue de Chantepoulet, CH-1211 Geneva 1 Switzerland

Telephone: +41 22 908 0488

Email: wspc2012@kenes.com; Website: <http://www.kenes.com/wspc>**30th International Congress of Psychology - ICP 2012**

Jul 22 - 27, 2012

Cape Town International Convention Centre, Cape Town, *South Africa*

Contact: Fatima Seedat, PO Box 989, Houghton 2041, South Africa

Telephone: 011 486 3322; Fax: 011 486 3266

Email: info@icp2012.com; Website: <http://www.icp2012.com/index.php?bodyhtml=home.html>**30th Annual Head to Toe Imaging Conference**

Dec 12 - 17, 2011

Hilton New York, New York, NY, *United States*

Contact: Marisa Costello, 462 First Ave, New York, NY

Telephone: 212-263-0724

Email: marisa.bruno@nyumc.org; Website: <http://www.med.nyu.edu/courses/cme/h2t11>**The 6th World Congress World Institute of Pain**

Feb 4 - 6, 2012

Miami Beach, FL, *United States*

Contact: Kenes International, 1-3 Rue de Chantepoulet PO Box 1726, CH-1211, Geneva 1 Switzerland

Telephone: +41 22 908 0488; Fax: +41 22 906 9140

Email: wip@kenes.com; Website: <http://www.kenes.com/wip>**Advanced Technologies & Treatments for Diabetes**Geneva, *Switzerland*

February 8 - 11, 2012

Contact: Kenes, 1-3, Rue de Chantepoulet,

Telephone: 4122908048; Fax: 4122906914

Email: attd@kenes.com; Website: <http://www.kenes.com/attd>**1st International Conference on Heart and Brain - ICHB 2012**Hotel Pullman Paris Montparnasse, Paris, *France*

Mar 1 - 3, 2012

Contact: Kenes International, 1-3 Rue de Chantepoulet, CH-1211 Geneva 1 Switzerland

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WHO-Facts Sheet

1. Obesity and Overweight
2. Antimicrobial Resistance
3. Visual Impairment and Blindness
4. Some 2.6 Million Babies Stillborn in 2009
5. Urgent Action Essential to Protect Malaria Therapies

Compiled and edited by
Babichan K Chandy

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1. OBESITY AND OVERWEIGHT

What are overweight and obesity?

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m²).

The WHO definition is:

- a BMI greater than or equal to 25 is overweight
- a BMI greater than or equal to 30 is obesity.

BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults. However, it should be considered a rough guide because it may not correspond to the same degree of fatness in different individuals.

Key facts

- Worldwide obesity has more than doubled since 1980.
- In 2008, 1.5 billion adults, 20 and older, were overweight. Of these over 200 million men and nearly 300 million women were obese.
- 65% of the world's population live in countries where overweight and obesity kills more people than underweight.
- Nearly 43 million children under the age of five were overweight in 2010.
- Obesity is preventable.

Facts about overweight and obesity

Overweight and obesity are the fifth leading risk for global deaths. At least 2.8 million adults die each year

as a result of being overweight or obese. In addition, 44% of the diabetes burden, 23% of the ischaemic heart disease burden and between 7% and 41% of certain cancer burdens are attributable to overweight and obesity.

Some WHO global estimates from 2008 follow.

- 1.5 billion adults, 20 and older, were overweight.
- Of these 1.5 billion overweight adults, over 200 million men and nearly 300 million women were obese.
- Overall, more than one in ten of the world's adult population was obese.
- In 2010, around 43 million children under five were overweight. Once considered a high-income country problem, overweight and obesity are now on the rise in low- and middle-income countries, particularly in urban settings. Close to 35 million overweight children are living in developing countries and 8 million in developed countries.

Overweight and obesity are linked to more deaths worldwide than underweight. For example, 65% of the world's population live in countries where overweight and obesity kill more people than underweight (this includes all high-income and most middle-income countries).

What causes obesity and overweight?

The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. Globally, there has been:

- an increased intake of energy-dense foods that are high in fat, salt and sugars but low in vitamins, minerals and other micronutrients; and
- a decrease in physical activity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization.

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- Changes in dietary and physical activity patterns are often the result of environmental and societal changes associated with development and lack of supportive policies in sectors such as health, agriculture, transport, urban planning, environment, food processing, distribution, marketing and education.

What are common health consequences of overweight and obesity?

Raised BMI is a major risk factor for noncommunicable diseases such as:

- cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2008;
- diabetes;
- musculoskeletal disorders (especially osteoarthritis - a highly disabling degenerative disease of the joints);
- some cancers (endometrial, breast, and colon).

The risk for these noncommunicable diseases increases, with the increase in BMI.

Childhood obesity is associated with a higher chance of obesity, premature death and disability in adulthood. But in addition to increased future risks, obese children experience breathing difficulties, increased risk of fractures, hypertension, early markers of cardiovascular disease, insulin resistance and psychological effects.

Facing a double burden of disease

Many low- and middle-income countries are now facing a "double burden" of disease.

- While they continue to deal with the problems of infectious disease and under-nutrition, they are experiencing a rapid upsurge in noncommunicable disease risk factors such as obesity and overweight, particularly in urban settings.
- It is not uncommon to find under-nutrition and obesity existing side-by-side within the same country, the same community and the same household.

Children in low- and middle-income countries are more vulnerable to inadequate pre-natal, infant and young child nutrition. At the same time, they are exposed to high-fat, high-sugar, high-salt, energy-dense, micronutrient-poor foods, which tend to be lower in cost. These dietary patterns in conjunction with low levels of physical activity, result in sharp increases in childhood obesity while undernutrition issues remain unsolved.

How can overweight and obesity be reduced?

Overweight and obesity, as well as their related noncommunicable diseases, are largely preventable. Supportive environments and communities are

fundamental in shaping people's choices, making the healthier choice of foods and regular physical activity the easiest choice, and therefore preventing obesity.

At the individual level, people can:

- limit energy intake from total fats;
 - increase consumption of fruit and vegetables, as well as legumes, whole grains and nuts;
 - limit the intake of sugars;
 - engage in regular physical activity;
 - achieve energy balance and a healthy weight.
- Individual responsibility can only have its full effect where people have access to a healthy lifestyle. Therefore, at the societal level it is important to:
- support individuals in following the recommendations above, through sustained political commitment and the collaboration of many public and private stakeholders;
 - make regular physical activity and healthier dietary patterns affordable and easily accessible to all - especially the poorest individuals.
 - The food industry can play a significant role in promoting healthy diets by:
 - reducing the fat, sugar and salt content of processed foods;
 - ensuring that healthy and nutritious choices are available and affordable to all consumers;
 - practicing responsible marketing;
 - ensuring the availability of healthy food choices and supporting regular physical activity practice in the workplace.

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2. ANTIMICROBIAL RESISTANCE

What is antimicrobial resistance?

Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was previously sensitive. Resistant organisms (they include bacteria, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist and may spread to others. AMR is a consequence of the use, particularly the misuse, of antimicrobial medicines and develops when a microorganism mutates or acquires a resistance gene.

Key facts

- Infections caused by resistant microorganisms often fail to respond to conventional treatment, resulting in prolonged illness and greater risk of death.

- About 440,000 new cases of multidrug-resistant tuberculosis (MDR-TB) emerge annually, causing at least 150,000 deaths.
- Resistance to earlier generation antimalarial medicines such as chloroquine and sulfadoxine-pyrimethamine is widespread in most malaria-endemic countries.
- A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA).
- Inappropriate and irrational use of antimicrobial medicines provides favourable conditions for resistant microorganisms to emerge, spread and persist.

Why is antimicrobial resistance a global concern?

AMR kills: Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness and greater risk of death.

AMR hampers the control of infectious diseases: AMR reduces the effectiveness of treatment because patients remain infectious for longer, thus potentially spreading resistant microorganisms to others.

AMR threatens a return to the pre-antibiotic era: Many infectious diseases risk becoming uncontrollable and could derail the progress made towards reaching the targets of the health-related United Nations Millennium Development Goals set for 2015.

AMR increases the costs of health care: When infections become resistant to first-line medicines, more expensive therapies must be used. The longer duration of illness and treatment, often in hospitals, increases health-care costs and the financial burden to families and societies.

AMR jeopardizes health-care gains to society: The achievements of modern medicine are put at risk by AMR. Without effective antimicrobials for care and prevention of infections, the success of treatments such as organ transplantation, cancer chemotherapy and major surgery would be compromised.

AMR threatens health security, and damages trade and economies: The growth of global trade and travel allows resistant microorganisms to be spread rapidly to distant countries and continents.

Facts on antimicrobial resistance

About 440,000 new cases of multidrug-resistant tuberculosis (MDR-TB) emerge annually, causing at least 150,000 deaths. Extensively drug-resistant tuberculosis (XDR-TB) has been reported in 64 countries to date.

Resistance to earlier generation antimalarial medicines such as chloroquine and sulfadoxine-

pyrimethamine is widespread in most malaria-endemic countries. Falciparum malaria parasites resistant to artemisinins are emerging in South-East Asia; infections show delayed clearance after the start of treatment (indicating resistance).

A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci.

Resistance is an emerging concern for treatment of HIV infection, following the rapid expansion in access to antiretroviral medicines in recent years; national surveys are underway to detect and monitor resistance.

Ciprofloxacin is the only antibiotic currently recommended by WHO for the management of bloody diarrhoea due to *Shigella* organisms, now that widespread resistance has developed to other previously effective antibiotics. But rapidly increasing prevalence of resistance to ciprofloxacin is reducing the options for safe and efficacious treatment of shigellosis, particularly for children. New antibiotics suitable for oral use are badly needed.

AMR has become a serious problem for treatment of gonorrhoea (caused by *Neisseria gonorrhoeae*), involving even "last-line" oral cephalosporins, and is increasing in prevalence worldwide. Untreatable gonococcal infections would result in increased rates of illness and death, thus reversing the gains made in the control of this sexually transmitted infection.

New resistance mechanisms, such as the beta-lactamase NDM-1, have emerged among several gram-negative bacilli. This can render powerful antibiotics, which are often the last defence against multi-resistant strains of bacteria, ineffective.

What drives antimicrobial resistance?

Inappropriate and irrational use of medicines provides favourable conditions for resistant microorganisms to emerge and spread. For example, when patients do not take the full course of a prescribed antimicrobial or when poor quality antimicrobials are used, resistant microorganisms can emerge and spread.

Underlying factors that drive AMR include:

- inadequate national commitment to a comprehensive and coordinated response, ill-defined accountability and insufficient engagement of communities;
- weak or absent surveillance and monitoring systems;
- inadequate systems to ensure quality and uninterrupted supply of medicines
- inappropriate and irrational use of medicines, including in animal husbandry;

- poor infection prevention and control practices;
- depleted arsenals of diagnostics, medicines and vaccines as well as insufficient research and development on new products.

Combat drug resistance: no action today, no cure tomorrow

The emergence of AMR is a complex problem driven by many interconnected factors; single, isolated interventions have little impact. A global and national multi-sectoral response is urgently needed to combat the growing threat of AMR.

WHO's response

WHO is engaged in guiding the response to AMR through:

- policy guidance, support for surveillance, technical assistance, knowledge generation and partnerships, including through disease prevention and control programmes;
- essential medicines quality, supply and rational use;
- infection prevention and control;
- patient safety;
- laboratory quality assurance.

WHO has selected combating antimicrobial resistance as the theme for World Health Day 2011. On this day, WHO issues an international call for concerted action to halt the spread of antimicrobial resistance and recommends a six-point policy package for governments.

WHO calls on all key stakeholders, including policy-makers and planners, the public and patients, practitioners and prescribers, pharmacists and dispensers, and the pharmaceutical industry, to act and take responsibility for combating antimicrobial resistance.

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3. VISUAL IMPAIRMENT AND BLINDNESS

Definitions

There are four levels of visual function, according to the International Classification of Diseases -10 (Update and Revision 2006):

- normal vision
- moderate visual impairment
- severe visual impairment
- blindness.

Moderate visual impairment combined with severe visual impairment are grouped under the term "low

vision": low vision taken together with blindness represents all visual impairment.

Key facts

- About 284 million people are visually impaired worldwide: 39 million are blind and 245 have low vision.
- About 90% of the world's visually impaired live in developing countries.
- Globally, uncorrected refractive errors are the main cause of visual impairment but in middle and low-income countries cataracts remain the leading cause of blindness.
- The number of people visually impaired from infectious diseases has greatly reduced in the last 20 years.
- 80% of all visual impairment can be avoided or cured.

The causes of visual impairment

Globally the major causes of visual impairment are:

- uncorrected refractive errors (myopia, hyperopia or astigmatism), 43 %
- cataract, 33%
- glaucoma, 2%.

Who is at risk?

Approximately 90% of visually impaired people live in developing countries.

People aged 50 and over

About 65 % of all people who are visually impaired are aged 50 and older, while this age group comprises about 20% of the world's population. With an increasing elderly population in many countries, more people will be at risk of age-related visual impairment.

Children below age 15

An estimated 19 million children are visually impaired. Of these, 12 million children are visually impaired due to refractive errors, a condition that could be easily diagnosed and corrected. 1.4 million are irreversibly blind for the rest of their lives.

Changes over the last twenty years

Overall, visual impairment worldwide has decreased since the early 1990s. This is despite an aging global elderly population. This decrease is principally the result of a reduction in visual impairment from infectious diseases through concerted public health action.

The global response to prevention of blindness

Globally, 80% of all visual impairment can be

prevented or cured. Areas of progress over the last 20 years include:

- governments establishing national programmes to prevent and control visual impairment;
- eye care services increasingly integrated into primary and secondary health care systems, with a focus on the provision of services that are available, affordable and high quality;
- campaigns to raise awareness, including school-based education; and
- stronger international partnerships, with engagement of the private sector and civil society.

Data over the last 20 years shows that there has been significant progress in preventing and curing visual impairment in many countries. Furthermore, there has been a massive reduction in onchocerciasis-related blindness as part of a significant reduction in the disease. This has been achieved through a number of successful international partnerships.

Specific achievements include Ghana and Morocco, both of whom have reported elimination of trachoma (2010 and 2007 respectively). Over the last decade, Brazil has been providing eye care services through the national social security system. Since 2009, China has invested over 100 million dollars in cataract surgeries. Oman has completely integrated eye care service provision in the primary health care framework over the last decade and since 1995 India has made available funds for eye care service provision for the poorest at district level.

WHO response

WHO coordinates the international efforts to reduce visual impairments.

It's role is to:

- develop policies and strategies to prevent blindness;
- to give technical assistance to Member States and partners;
- to monitor and evaluate programmes; and
- to coordinate international partnerships.

In 2009, the World Health Assembly approved the '2009-13 Action Plan for the Prevention of Avoidable Blindness and Visual Impairment', a roadmap for Member States, WHO Secretariat and international partners.

WHO works to strengthen national and country-level efforts to eliminate avoidable blindness, help national health care providers treat eye diseases, expand access to eye health services, and increase rehabilitation for people with residual visual impairment. Building and strengthening health systems is a particular area of focus.

WHO leads an international alliance of governments, private sector and civil society organizations. The aim

of this partnership is to eliminate blinding trachoma from the world by the year 2020.

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4. SOME 2.6 MILLION BABIES STILLBORN IN 2009

New global and country estimates published in Lancet Series

Some 2.6 million stillbirths occurred worldwide in 2009, according to the first comprehensive set of estimates published in April 2011 in a special series of The Lancet medical journal.

Every day more than 7 200 babies are stillborn – a death just when parents expect to welcome a new life – and 98% of them occur in low- and middle-income countries. High-income countries are not immune, with one in 320 babies stillborn – a rate that has changed little in the past decade.

The new estimates show that the number of stillbirths worldwide has declined by only 1.1% per year, from 3 million in 1995 to 2.6 million in 2009. This is even slower than reductions for both maternal and child mortality in the same period.

The five main causes of stillbirth are childbirth complications, maternal infections in pregnancy, maternal disorders (especially hypertension and diabetes), fetal growth restriction and congenital abnormalities.

When and where do stillbirths occur?

Almost half of all stillbirths, 1.2 million, happen when the woman is in labour. These deaths are directly related to the lack of skilled care at this critical time for mothers and babies.

Two-thirds happen in rural areas, where skilled birth attendants – in particular midwives and physicians – are not always available for essential care during childbirth and for obstetric emergencies, including caesarean sections.

The stillbirth rate varies sharply by country, from the lowest rates of 2 per 1000 births in Finland and Singapore and 2.2 per 1000 births in Denmark and Norway, to highs of 47 in Pakistan and 42 in Nigeria, 36 in Bangladesh, and 34 in Djibouti and Senegal. Rates also vary widely within countries. In India, for example, rates range from 20 to 66 per 1000 births in different states.

It is estimated that 66% – some 1.8 million stillbirths – occur in just 10 countries: India, Pakistan, Nigeria, China, Bangladesh, Democratic Republic of the Congo,

Ethiopia, Indonesia, Afghanistan and the United Republic of Tanzania.

Comparing stillbirth rates in 1995 to 2009, the least progress has been seen in Sub-Saharan Africa and Oceania. However, some large countries have made progress, such as China, Bangladesh, and India, with a combined estimate of 400,000 fewer stillbirths in 2009 than in 1995. Mexico has halved its rate of stillbirths in that time.

"Many stillbirths are invisible because they go unrecorded, and are not seen as a major public health problem. Yet, it is a heartbreaking loss for women and families. We need to acknowledge these losses and do everything we can to prevent them. Stillbirths need to be part of the maternal, newborn and child health agenda," says Dr Flavia Bustreo, WHO's Assistant Director-General for Family and Community Health.

Well-known interventions for women and babies would save stillbirths too

The Series shows that the way to address the problem of stillbirth is to strengthen existing maternal, newborn, and child health programmes by focusing on key interventions, which also have benefits for mothers and newborns.

According to an analysis to which WHO contributed in The Lancet Stillbirth Series, as many as 1.1 million stillbirths could be averted with universal coverage of the following interventions:

Comprehensive emergency obstetric care	696 000
Syphilis detection and treatment	136 000
Detection and management of fetal growth restriction	107 000
Detection and management of hypertension during pregnancy	57 000
Identification and induction for mothers with >41 weeks gestation	52 000
Malaria prevention, including bednets and drugs	35 000
Folic acid fortification before conception	27 000
Detection and management of diabetes in pregnancy	24 000

Strengthening family planning services would also save lives by reducing the numbers of unintended pregnancies, especially among high-risk women, and thereby reduce stillbirths.

"If every woman had access to a skilled birth attendant – a midwife, and if necessary a physician – for both essential care and for procedures such as emergency caesarean sections, we would see a dramatic decrease in the number of stillbirths," says Dr Carole Presern, Director of The Partnership for Maternal, Newborn & Child Health (PMNCH), and a trained midwife.

Stillbirths overlooked

Despite the large numbers, stillbirths have been relatively overlooked. They are not included in

the Millennium Development Goals for improving maternal health and reducing child mortality.

The estimates were generated using a statistical model that took records of births and deaths (known as 'vital registration' data) from 79 countries, surveys from 39 countries, and studies from 42 countries. Weak vital registration systems, especially in the regions where most stillbirths occur, limit the availability of data and hamper the calculation of precise estimates. Vital registration systems must be improved so that all stillbirths are counted.

The new estimates aim to improve knowledge about the extent of the problem, and draw public and professional attention to stillbirths as a significant global public health issue.

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5. URGENT ACTION ESSENTIAL TO PROTECT MALARIA THERAPIES

The world risks losing its most potent treatment for malaria unless steps are quickly taken to prevent the development and spread of drug resistant parasites, according to a new action plan released in January 2011 by the World Health Organization (WHO) and Roll Back Malaria partnership (RBM).

The Global Plan for Artemisinin Resistance Containment outlines the necessary actions to contain and prevent resistance to artemisinins, which are the critical component of artemisinin-based combination therapies (ACTs), the most potent weapon in treating falciparum malaria, the deadliest form of the disease. Resistance to artemisinins has already emerged in areas on the Cambodia-Thailand border. Although ACTs are currently more than 90% efficacious around the world, quick action is essential. If these treatments fail, many countries will have nothing to fall back on.

"The usefulness of our most potent weapon in treating malaria is now under threat," said Dr Margaret Chan, WHO Director-General. "The new plan takes advantage of an unprecedented opportunity in the history of malaria control: to stop the emergence of drug resistance at its source and prevent further international spread. The consequences of widespread artemisinin resistance compel us to seize this opportunity."

The global plan aims to contain and prevent artemisinin resistance through a five-step action plan:

1. Stop the spread of resistant parasites

A fully funded and implemented malaria control agenda, as outlined in the Global Malaria Action Plan, would address many of the needs for the containment and prevention of artemisinin resistance. However, additional funding will be needed to stop the spread of resistant parasites in areas where there is evidence of artemisinin resistance. The global plan estimates that it will cost an additional US\$ 10 – 20 per person in areas of confirmed resistance (Cambodia-Thailand border) and US\$ 8 – 10 per person in the at-risk areas of the Greater Mekong area.

2. Increase monitoring and surveillance for artemisinin resistance

WHO estimated in 2010 that only 31 of the 75 countries that should be conducting routine testing of the efficacy of ACTs actually did so. There is a risk of artemisinin resistance emerging silently in areas without ongoing surveillance.

3. Improve access to malaria diagnostic testing and rational treatment with ACTs

These therapies are frequently used to treat causes of fever other than malaria. Unnecessary use of ACTs can increase the risk of resistance. In order to reduce the number of patients who do not have malaria taking the therapies, WHO recommends diagnostic testing of all suspected malaria cases prior to treatment.

4. Invest in artemisinin resistance-related research

There is an urgent need to develop more rapid techniques for detecting resistant parasites, and to develop new classes of antimalarial medicines to eventually replace the ACTs.

5. Motivate action and mobilize resources

The success of the global plan will depend on a well coordinated and adequately funded response from many stakeholders at global, regional and national levels.

“Effective containment of artemisinin resistance will significantly improve our capability to sustain current control achievements at country level,” said Professor Awa Coll-Seck, Executive Director of the Roll Back Malaria Partnership. “We now have a coordinated plan to stop the spread of resistant parasites, but we need additional funding to fully implement it,” Coll-Seck reminded the international donor community.

WHO estimates that the number of malaria cases has fallen by more than 50% in 43 countries over the past decade. A recent modeling analysis of malaria prevention in 34 African countries estimates that more than 730 000 lives were saved between 2000 and 2010; nearly three quarters of them since 2006, when the use of both insecticide treated mosquito nets and ACTs became more widespread. The loss of ACTs as an effective treatment would likely result in a significant increase in malaria-related deaths.

“We have made tremendous progress over the past decade in the fight against malaria,” noted Dr Robert Newman, Director of the WHO Global Malaria Programme. “If we are to sustain these gains and achieve the health-related Millennium Development Goals, then it is essential that we work together to overcome the threat of artemisinin resistance.”

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