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Editorial

Daring Heroes of the Distant Past

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“One man with courage makes a majority.”
Andrew Jackson

Our younger generation in medicine looks up to the present day divine interventionalists and the heroic surgeons, who are all over the media, both print and electronic, to emulate and follow on their footsteps. Modern medicine is suffering because we have been following what others have been doing elsewhere. Such “copy-cat” procedures and interventions do not take knowledge forwards in any field. We need to progress by taking the present inadequate knowledge forwards in modern medicine. That needs a different kind of research, called refutative research, wherein one tries to refute false dogmas that do not stand on very firm grounds. We should not waste time copying others by repeating known facts repetitively.

History of modern medicine is replete with such mistakes. One example would suffice. It was in the year 127 AD that the great guru of medicine of those days, Galen, thought that blood circulated from the liver. This was repeated by all and sundry for well over one thousand five hundred years till 1628 AD when a thinker refuted that claim and showed that blood circulates from the heart - *De Motu Cordis* of William Harvey. Many such instances could be cited. One, therefore, needs look back at the past history to learn from it and stimulate the latent curiosity in our younger generation, lest one should be condemned to relive history. We have no dearth of “copy-cats” in modern medicine who claim glory and fame copying others and not taking knowledge forwards. Some of them are labeled heroic doers; the hero, however, is the hapless patient who has subjected himself for their misadventures. If the patient survives they claim all the credit; if, on the other hand, the patient meets his maker, we could always blame fate.

Here is the true story of one such real daring hero of the distant past, who started life as a poor boy and ended up getting the Nobel Prize. He refuted the existing wisdom of his time by his daring. The notable feature of his daring is his offering himself as the experimental subject instead of using a poor patient. Werner Forssmann in his brilliant book *Experiments on Myself*, first published in German in 1972 and, later translated to English by Hillary Davies in 1974, published by Saint Martin’s Press in New York,[1] echoes the sentiments expressed by me earlier thus: “In my life time powerful men have managed to determine not only political events but also peoples’ personal lives and the progress of science by practising deception. Their methods were sometimes primitive but always effective” (Author’s text in italics).

This is more so in the present time when the whole field of modern medicine is vitiated by deception of the highest order. A recent daring report from the US showed that more than 225,000 people died in one year thanks to the medical establishment in the name of doing good to the public.[2] Doctors have been one of the leading causes of death in the US followed by heart attacks and cancer! Forssmann’s life changed because of the events at that time. The First World War made him hate the monarchy and the Second World War made him an ardent pacifist. His seniors, many of them celebrated medical men of his time, were men with feet of clay. The greatest of them all at that time (1929 AD) was the celebrated Herr Geheimrat Sauerbruch, the then great general and cardiac surgeon, who went on operating well into his 80s killing hundreds of hapless patients.
but, patients still flocked to him even in his home where he operated upon them on his kitchen table even after the hospital in the then Mecca of German surgery, the Charite in Berlin, compelled him to retire gracefully.

When the young Forssmann knocked on the door of the great man’s office, his secretary, Frau Rogetzki, looked at him from top to bottom and stopped polishing her nails to tell him: “In this hospital one does not present oneself to the Herr Geheimrat; one waits to be summoned.” Those were the days. The present readers might feel that things have not changed very much, in all these years. Getting a job at the Charite was a very great achievement those days. It would not have been possible for the young Forssmann to get anywhere near there, although he studied in the famous medical school in Berlin’s Friederich Wilhelm University. He was brought up by his mother after his father’s death in the First World War. He and his mother lived on a hand-to-mouth existence, when all the other students came from very affluent families. His teachers, some of them great men of learning, were the ones that motivated him to be what he became later in life.

Having seen the ravages of the two world wars and the rise of Hitler, Forssmann later in life, became a citizen of the Federal Republic of Germany. Forssmann is known for his daring act of challenging the medical taboo of his time that the heart can never be entered into, to study its function. Determined and very courageous, Forssmann, then a surgeon in training, opened a vein in his forearm, inserted the tip of a long, thin tube, and pushed it along the vein into his own heart. Standing in front of a fluoroscope machine he could see the tip of the catheter in his heart and then he got an X-ray taken to record the tube’s presence in the heart for the first time in man, when at a time such an act was thought to be fatal.

Forssmann did not invent the method, though. In the year 1840 the great French physiologist, Claude Bernard, developed the technique for use in animals. Later physiologists, Chauveau, Marey, A. Fick, and N Zuntz developed it further and studied the pressures in the various chambers of the heart as also analyzed the blood samples from those chambers. Despite these reports Forssmann was severely criticized for what he did and was ignored by those powers-that-be in medicine in Germany those days. Undaunted by the hostility Forssmann went on to inject a radio-opaque dye into his own heart and larger vessels and laid the foundation for what we now call angiography. This initiative was picked up by others elsewhere and the methods were perfected to the level that we see today. Discouraged by strong opposition Forssmann stopped being a researcher and trained to be an urologist and practised that art in a small place in Rhineland.

Fate finally rewarded him, nearly quarter of a century later, when he was awarded the Nobel Prize for Medicine and Physiology along with two other Americans who had later perfected the technique. When a reporter went to inform Forssmann of his getting the Nobel, he is said to have joked: “I feel like a village parson who has just learnt that he has made the Bishop.” As a young surgeon Forssmann had to bear the brunt of the war and was imprisoned by the Russians from where he escaped under fire to cross the river Elbe to finally practise urology in a small Rhineland spa. After getting the Nobel he tried to establish himself as the chief surgeon in a voluntary hospital without much success. This book gives the reader a varied picture of a young brilliant student, a nationalist to the core, a dissenter who dared to risk his career for finding the truth, and a man endowed with abundant physical courage if not political sagacity. His wife, also a physician, was a quiet lady who mothered their six children. She was also a wise and dignified lady. They eventually retired to a quiet life in a large cottage in the Black Forest.

Before I close, I must give the reader the first hand version of what happened that fateful day in the operating theatre of Eberswalde, a small Prussian town northeast of Berlin. This account would show the rare courage that the man exhibited risking his own life, the real heroic surgeon-the hero being himself. With great difficulty, and after much influence (even those days!) Frossmann managed to get an unpaid job as a surgeon under Dr. Richard Schneider, a kind hearted man known to Forssmann’s aunt. When Frossmann presented his idea of studying the heart’s function more clearly by entering the heart with a catheter, Schneider mildly rebuked him and passed an order that Frossmann should not be let into any theatre.

Not to be put off by such acts, Frossmann started to prowl around a beautiful theatre Nurse Gerda Ditzen “like a sweet toothed cat around the cream jug”. He wanted to slyly carry out his black deed during the afternoon siesta when the whole hospital would be sleeping. Nurse Gerda was suspicious in the beginning but later, after much flirting, she became very friendly and almost became his close confidant. However, Forssmann did not have romantic ideas at all. She, on the contrary, was living in a romantic world. He used to take her out, give her books to read and one day told her his real plans. Immediately she became very serious and refused point blank.

He told her one day “Nurse Gerda, you need know nothing about what I am going to do. But supposing I were to do the experiment it would be
“Absolutely” he answered. “All right then do it to me, I put myself in your hands,” she said.

That is what he wanted. “Well, you will be the first person in the world to have the catheter in your heart” he told her.

His ruse was to get all the instruments. When all the instruments were laid on the table he asked her to lie down. He firmly tied her hands and legs to the operating table and told her his real intention was to do it on himself with her safely tied down to the table. Of course, history was made in Eberswalde that fateful day in 1929. Rest is history.

Here is the story of a great surgeon, whose extraordinary talents were not recognized by his seniors, many of whom did not allow him to publish his data saying that he had no right to publish. They also told him, led by Sauerbruch himself, that he has to include them in the publication, reminiscent of today’s world. The only person who encouraged him after the act was Schneider, who had a soft corner for this young man. With all this the poor Forssmann had to go into oblivion in Germany until the Nobel Committee picked him to share this great honour with two Americans. Lesser mortals have got away with the Nobel for not so good reasons. Such is the power of mystery and falsehood. However, people like Forssmann are rare and they are the real heroes of the distant past who could motivate generations of young men and women in medicine. May their tribe increase? The message Forssmann gave to the world, in the words of a friend of mine, is “Learn to be wise; if not, you will be otherwise.”

“Opinions cannot survive, if one has no chance to fight for them.”

Thomas Mann

REFERENCES


Review Article

The Crisis of Lifestyle Conditions in the Middle East With Special Attention to Kuwait: An Unequivocal Evidence-based Call to Action

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ABSTRACT

Given the prevalence of lifestyle conditions in Kuwait and their considerable social and economic burdens, this article is an urgent call to health care practitioners for action. To reverse this trend, several relatively simple changes in orientation toward practice by health care practitioners are described. These include collectively advocating a bold approach to community health through social and health policy; a commitment to a conceptual framework of health care versus perseverance of an illness care model; assessing health risk in every patient, exploiting evidence-based non-drug and non-surgical interventions for the prevention of lifestyle conditions and in some cases ‘cure’ as well as their management, and practicing within the paradigm of a health care team whereby the expertise of non-invasive practitioners and behavior change specialists is exploited, and patients are systematically followed over time. By adopting such evidence-based strategies to address health priorities in Kuwait, health care professionals can assume a leadership role within the global community in reversing the prevalence of the leading causes of morbidity and mortality, thereby enabling the medical community to use its skills and expertise more cost effectively. In turn, the demand for simply symptomatic management of lifestyle conditions as well as the need for physician visits would be reduced. Particular strengths that contribute to Kuwait being strategically well positioned to lead the assault on lifestyle conditions include the cumulating knowledge base on the health of Kuwaitis and it being an Islamic country. Health education through religion is an underutilized yet powerful resource that could empower Kuwaitis to reverse the prevalence of lifestyle conditions and their associated burdens.

KEY WORDS: cancer, cure, diabetes, health education, heart disease, hypertension, Islamic health perspectives, lifestyle conditions, management, obesity, prevention, smoking-related conditions, stroke

INTRODUCTION

The leading causes of morbidity and mortality in the Middle East include ischemic heart disease, smoking-related conditions, hypertension and stroke, diabetes, obesity and cancer. The leading causes of death in Kuwait are shown in Table 1[1]. Obesity and diabetes are particularly pandemic in Kuwait and their multisystem consequences to health and well-being within the country have reached critical proportions[2,3]. Lifestyle conditions are projected to predominate throughout the 21st century and contribute increasingly to the social and economic burdens of disease. Their predominance has increased with economic development throughout the region with a shift from traditional diets and active lifestyles to western dietary patterns, sedentary lifestyles and cigarette smoking. The World Health Organization has declared that lifestyle conditions and their sequelae are largely preventable[4]. Despite the considerable evidence supporting this assertion, adopting healthy lifestyle practices or changing these when health risk factors manifest has been challenging for the general public to achieve. Health care practitioners however are committed to excellence in their care and in first doing ‘no harm’. With appropriate clinical competence in effecting health behavior change and referring to others with greater expertise as needed, health care practitioners can empower individuals and their families to value their health by practicing healthy lifestyles and maintain a high quality of life throughout the life cycle with minimal end-of-life morbidity.

This article describes some simple changes in practice paradigm that can be readily incorporated by the busy practitioner to effect a reversal of the
devastating health trends related to morbidity associated with lifestyle choices\(^\text{(5,6)}\). Examples of 21\(^{st}\) century clinical competencies include identification of key risk factors and their modification. Identifying lifestyle risk factors has the advantage of enabling the practitioner to specifically address the underlying causes of lifestyle conditions rather than simply their signs and symptoms. With a concerted effort across health care professionals, physicians will be able to use their time to better advantage and achieve superior outcomes. Partnering with other health care team members who are proficient in effecting health behavior change is essential in addressing the health priorities of the 21\(^{st}\) century. Finally, this article describes how Kuwait is uniquely positioned to lead in the assault on lifestyle conditions given the growing body of knowledge on lifestyle conditions in Kuwaitis and that health education through religion has been largely untapped.

**RISK FACTORS AND THEIR MODIFICATION**

While the evidence causally linking smoking, poor nutrition, inactivity and stress with lifestyle conditions has been unequivocally established, effecting change in health behavior practices has proven to be challenging in health care. In one recent study, only 5\% of survivors of cancer in the US followed the lifestyle recommendations\(^\text{(7)}\). Further, aggressive control of risk factors and the prescription of exercise in conjunction with pharmacological interventions have been well established to prevent and remediate cardiovascular symptoms and events\(^\text{(8)}\). Lack of adherence to recommendations to prevent and in some cases ‘cure’ as well as manage the manifestations of lifestyle conditions needs to be a primary focus of health care in every person and patient. To effect health behavior change, health risks need to be quantified with tools that are sensitive and detect change over time. Examples of such tools are described in the relevant section below.

The relationship between lifestyle and chronic lifestyle conditions is shown in Table 2. Lifestyle conditions share common risk factors, hence, comorbidity is common. These conditions can no longer be considered afflictions of adults. Children share the family experience of dietary and activity patterns, and have increased probability of smoking, if one or both parents smoke. Thus, children today are likely to have one or more risk factors of one or more lifestyle conditions. Thus, they are at increased risk of manifesting one or more lifestyle conditions in adulthood. This trend supports that pediatrics as a health specialty needs to screen for these risk factors and address them early.

Health behavior change is the quintessential clinical competency of the 21\(^{st}\) century health care practitioner. To integrate this clinical competence, health care professionals need tools to effect such change over the long as well as short-term course. Drawing on Islamic teachings may be a powerful tool in Islamic countries and this is described in the last section of this article. Initially, however, the individual’s readiness to change his or her health behavior needs to be established. The five stages include pre contemplative (the patient is not thinking about changing a specific health behavior at this time), contemplative (thinking about changing), preparation (preparing to change), action (participating in the requisite positive health behaviors), maintenance (reached health goals and maintaining healthy practices) and relapse (achieved health goals but health behaviors have relapsed)\(^\text{(12)}\). Recognition of his or her stage of readiness to change a deleterious health behavior conveys to the patient that he or she has a choice. Exercising a choice shifts responsibility for health appropriately to the individual from the health care professional and thereby enhances the patient’s sense of self-efficacy and power with respect to health and well-being.

**TOOLS FOR RISK FACTOR ASSESSMENT AND EVALUATION**

Tools to assess risk factors and evaluate the success of lifestyle modification intervention need to be incorporated into the baseline health status profile of every patient and in the health status profile of employees in the workplace and children at school. Various tools are available for clinical use for assessment of health risk factors and their evaluation over time. The Harvard School of Public Health, for example, has developed clinically-friendly disease risk assessment for several lifestyle conditions which are designed to be easily completed on-line\(^\text{(13)}\). This tool shows the health care practitioner and the patient the patients’ relative

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<td>1</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>2</td>
<td>Hypertensive heart disease</td>
</tr>
<tr>
<td>3</td>
<td>Road traffic accidents</td>
</tr>
<tr>
<td>4</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>5</td>
<td>Perinatal conditions</td>
</tr>
<tr>
<td>6</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>7</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>8</td>
<td>Lower respiratory infections</td>
</tr>
<tr>
<td>9</td>
<td>Nephritis and nephrosis</td>
</tr>
<tr>
<td>10</td>
<td>Breast cancer</td>
</tr>
</tbody>
</table>


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risk with a colorful chart which can be an effective teaching and learning tool. The multiple-risk-factor assessment for health professionals reported by Grundy and colleagues assesses cardiovascular risk in men and women based on six questions including age, total cholesterol, HDL, systolic blood pressure, diagnosis of diabetes and smoking behavior\[14\]. This test is easy to administer but does require blood work which contributes to its predictive validity. Relative and absolute risk estimates are displayed in charts for men and women. Comparable to the Harvard School of Public Health disease risk assessment, this multiple-risk-factor assessment tool has a color key to illustrate to the patient his or her relative risk ranging from green or below average risk to red or high risk. The results of these questionnaires provide a useful index of an individual’s overall health and demonstrate to the patient a shift in absolute and relative health risk. Norms for people in the Middle East however have not yet been published. Thus the results need to be considered in this light. Although translation into Arabic as well as other languages needs to be considered, English is the common language of health care in Kuwait. Therefore these questionnaires can be completed by the health care practitioner.

### Table 2: Modifiable risk factors of the lifestyle conditions (modified from references\[8-11\])

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cardiovascular Disease</th>
<th>Cancer</th>
<th>Obstructive Lung Disease</th>
<th>Stroke</th>
<th>Diabetes</th>
<th>Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>X</td>
<td></td>
<td>X († risk of all-cause cancer*)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Obesity</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nutrition</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>High BP</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dietary fat*/Blood lipids</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Elevated glucose levels</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* Smoking is not only related to cancer of the nose, mouth, airways, and lungs, but it increases the risk of all-cause cancer.
**Partially saturated, saturated, and trans fats are the most injurious to health.

### The 21st Century Health Care Practitioner

#### Practicing as a health care team: The new paradigm of care

The complex health care priorities of the 21st century can best be addressed through the partnership of a team of health care professionals. Patients today have one or more risk factors for one or more lifestyle conditions, their manifestations, or both. These demands therefore exceed what a single practitioner is able to provide in terms of comprehensive lifelong health and care. Complex co-morbidity often associated with the chronic lifestyle conditions has become the norm. For this reason, the contemporary team needs to include counselors, dieticians, nurses, occupational therapists, personal trainers, physical therapists, psychologists as well as traditional team members, namely, physicians, surgeons and pharmacists. Physical therapists in particular are non-invasive practitioners who exploit non-drug and non-surgical interventions as much as possible. Physical therapists are well qualified to prescribe health behavior change interventions including health education and physical activity as interventions while partnering with the physician and other team members to prevent lifestyle conditions, in some cases ‘cure’ as well as manage them. Examples of ‘curing’ lifestyle conditions with non-invasive strategies are the reversal of atherosclerosis with non-invasive interventions\[15,16\] and the reversal of diabetes\[7,18\] and hypertension\[19,20\]. The inclusion of the physician is critical in the management of patients with non-invasive interventions to ensure that medications are weaned commensurate with improvement and for re-assessment in potential surgical cases to establish whether surgery remains indicated. Examples of the latter include the need for orthopedic surgery after significant weight loss or for cardiac surgery with improvement of coronary perfusion.

#### Patients in charge of their health

Empowering patients and their families is the hallmark of 21st century health care rather than the relatively disempowering care associated with the more patriarchal system that predominated in the 20th century. Only the patient can effect change in his or her health with information, advocacy, coaching, and follow-up. Recent evidence based on national data supports that Kuwaitis value such a consultative and team based model of care in which the patient is central and his or her input is sought and valued\[21,22\]. Furthermore, physicians are overextended in terms of their time, and
physical and mental capacities to provide care for largely preventable conditions. Risk reduction of lifestyle conditions and their severity would enable physicians to use their time and expertise to greater advantage.

CONTEMPORARY MEASURES AND OUTCOMES AND THEIR RATIONALE

Smoking status

Given smoking is the leading cause of preventable death\(^[23]\) and that it exacts a significant toll on Kuwait’s health care system\(^[24]\), smoking cessation needs to be a health priority in every smoker (both for the health of the family and individual). Specific details of the smoking history need to be sufficiently quantified to serve as outcome measures over time as well as fundamental components of an assessment. Table 3 illustrates how smoking behavior can be systematically recorded to facilitate the use of this information to assess change in smoking behavior over time. Substantial evidence supporting the health benefits of cessation of smoking can provide an essential incentive to the smoker to quit. Table 4 shows examples of evidence-based probabilities for reducing health risk over time.

Table 3: Smoking behavior assessment and evaluation tool

<table>
<thead>
<tr>
<th>History</th>
<th>Date</th>
<th>Date</th>
<th>Date</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>What do you smoke?</td>
<td>PC</td>
<td>PC</td>
<td>PC</td>
<td>PC</td>
</tr>
<tr>
<td>How many cigarettes a day do you smoke on average?</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Have you tried to quit?</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>If yes, how many times have you quit?</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>For how long were you successful?</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
</tbody>
</table>

Table 4: Evidence-based probabilities for reducing health risk over time

In addition to effecting smoking cessation in individuals who smoke, health care professionals need to advocate aggressively for social and health policies designed to target smokers regarding the hazards of smoking and to target school children prior to their experimenting with smoking\(^[28,29]\). In a recent study in Kuwaiti health care workers, smoking prevalence was high, a finding that was inconsistent with the needs of exemplary role models for their patients\(^[30]\). The investigators recommended comprehensive tobacco control laws with bans on tobacco advertising, smoke-free public places, large health warnings signs and health education campaigns. There is evidence throughout Kuwait that some of these recommendations have been acted upon in recent years. Finally, sheesha smoking is a cultural activity prevalent throughout the Middle East. However, there are relatively few studies on its prevalence and health effects. One study of student teachers in Kuwait identified it as a concern in this group who serve as role models for children\(^[31]\). Recommendations for addressing this issue in university and college students as well as young children were made.
Body composition

Measures that complement health risk assessment include body mass index [(weight (kg) / height (m²)], waist circumference, and waist-to-hip ratio\[^{32}\]. Self-reported height and weight tend to be over and under estimated respectively. Thus, these need to be measured in a standardized manner. The normal range of body mass index is 18.5 - 24.9, overweight is 25 - 29.9, and obese is 30 and over. Health risk increases correspondingly as body mass index exceeds 25. Waist circumference should be less that 90 cm in men and less than 84 cm in women\[^{33,34}\]. Waist-to-hip ratio should be less that 0.9 in men and less than 0.85 in women\[^{35}\]. Increased waist girth is associated with increased risk of cardiovascular disease, and particularly with increased waist-to-hip ratio. These measurements provide essential health risk assessment data, standardized outcome and evaluation measures, and prediction of health risk, and provide essential feedback to the patient in terms of effectiveness of lifestyle modification efforts.

Patients who are overweight have a high risk of being hypertensive\[^{36}\]. A study of Kuwaitis attending a primary health care facility identified that obesity and hypertension was typically coupled with poor diets and lack of exercise. Thus, intensive programs need to be targeted toward people who are obese as well as individualized programs prescribed for their specific needs, and long-term follow-up programs implemented.

Blood sugar and HbA1C

Blood sugar needs to be routinely taken in addition to glycosolyated hemoglobin (HbA1C), an established index of glycemic control\[^{41}\]. Poor control has recently been associated with increased oxidative stress which is known to increase the risk of other lifestyle conditions\[^{42}\].

The World Health Organization advocates an integrated approach exploiting cost-effective measures to prevent common health risks\[^{43,44}\]. In particular, one report stated that ‘it is unacceptable that so much disability and death are caused by leg amputation, when the solutions are clear and affordable’ and further ‘small investments in prevention and education can mean fewer leg amputations, increased quality of life for individuals and dramatic reductions in health care costs’. Retinopathy has been identified recently as the leading cause of visual impairment in Kuwait\[^{45}\]. Factors associated with progressive retinopathy included insulin treatment, duration of diabetes, and acceptance of elevated blood pressure with age, several authorities acknowledge systemic blood pressure less 140/90 mmHg as ideal\[^{37}\]. In Kuwait, hypertension has become a health priority for young as well as middle-aged adults given its well-documented multi-system consequences\[^{38}\]. Blood pressure measurement need to conform to standard measurement procedures to be valid and reliable\[^{39}\]. Poor blood pressure control in a cohort of people who are hypertensive in Kuwait has been attributed to poor adherence to lifestyle recommendations and medications\[^{40}\].

### Table 4: Evidence-based short- and long-term health benefits of quitting smoking

<table>
<thead>
<tr>
<th>Stages of Benefit</th>
<th>Type of Health Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Benefits</td>
<td>Healthier family; Quitting smoking removes harmful environmental tobacco smoke that pollutes non-smokers’ breathing space.</td>
</tr>
<tr>
<td>Benefit after 1 year</td>
<td>Increased risk of ischemic heart disease decreased 50%</td>
</tr>
<tr>
<td>Benefit after 3 years</td>
<td>Risk of heart disease is declining to levels similar to lifelong non-smokers</td>
</tr>
<tr>
<td>Benefits after 5 years</td>
<td>Risk of cancers of the oral cavity and esophagus reduced 50%</td>
</tr>
<tr>
<td>Benefit after 10 years</td>
<td>Risk of lung cancer decreased 50 to 70%</td>
</tr>
<tr>
<td>Benefits after 15 years</td>
<td>Risk of ischemic heart disease is similar to lifelong non-smoker</td>
</tr>
</tbody>
</table>

References: \[^{25-27}\]
age at examination, HbA1C, systolic blood pressure, cholesterol, triglyceride and microalbumin. Hence, these warrant assessment and on-going evaluation including HbA1C in patients with blood sugar disorders.

**ISLAM AND IMPLICATIONS FOR HEALTHY LIFESTYLE**

Effecting lifestyle behavior change needs to consider cultural context. Otherwise, methods for effecting such change will be ineffective. The literature on health behavior change is usually specific to a given culture. Thus this factor may not be mentioned explicitly within a given study. In Kuwait, as an Islamic country, religious teachings can be used to effect behavior change based on verses from the Quran and Haddith supporting healthy lifestyle practices (e.g., guidance with respect to eating in moderation, being physically active, not smoking). The Amman Declaration on an Islamic Perspective on Health supported and published by the World Health Organization is an important resource for the health care practitioner and patient to guide healthy living practices in Islamic countries.\(^{[46,47]}\)

**CONCLUSION**

The 21\(^{st}\) century is hallmarked by lifestyle conditions which are associated with substantial social and economic burdens in the countries of the Middle East including Kuwait. Epidemiologic trends show that not only have these conditions increased in prevalence but they are being detected and are manifesting at younger ages. Furthermore, these conditions complicate the course and outcome of other conditions including other chronic long-term conditions, and their response to medical and surgical intervention. This article describes the need for the 21\(^{st}\) century health care practitioner to be clinically competent with respect to risk factor assessment in every patient and basic recommendations to effect health behavior change. In addition, 21\(^{st}\) century practice calls for team work to address complex co-morbidity and effect life-long health. Specifically, physicians need to work closely with non invasive practitioners such as physical therapists to exploit non-drug and non-surgical interventions (health education and physical activity). Although drug and surgical interventions may help to offset some troublesome symptoms, addressing the causes of these conditions through lifestyle modification would result in superior outcomes including prevention, in some cases ‘cure’ as well as management of these conditions. Further, healthy lifestyle practices within families would ensure that the risk to children during their childhood and adulthood is minimized. Minimizing the effects of lifestyle conditions not only holds the promise of improved function, employability, reduced absenteeism, and reduced social and economic burdens, but improved mental health, subjective sense of well being and quality of life. It behooves every health care practitioner in Kuwait including physicians and physical therapists who specialize in non-drug and non-surgical solutions as much as possible, to work as a team in reducing health and disease risk from lifestyle conditions, in some instances ‘curing’ these (e.g., reversing atherosclerosis, hypertension, obesity and type 2 diabetes) as well as optimizing management outcomes and functional capacity. With the shift in 21\(^{st}\) century health care practice that is indicated by contemporary health care priorities, physicians will be able to spend their time and use their expertise to better advantage. As an Islamic country, Kuwait is in a strategic position in the Middle East to lead the way in this initiative and serve as a model to other Islamic countries.

**REFERENCES**

Epidemiology and significance of major risk factors for cardiovascular diseases in the Middle East


Original Article

The Relation between Salt Intake and Blood Pressure among Iranians

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1Medical Education Research Center, Isfahan University of Medical Sciences, Iran
2Cardiovascular Research Center, Isfahan University of Medical Sciences, Iran
3Isfahan University of Medical Sciences, Iran


ABSTRACT

Objectives: To determine the mean 24 hr urinary sodium (UNa) and chloride (UCl) excretion, and the association between these variables and blood pressure, since studies on the effect of habitual dietary salt intake and some electrolytes on blood pressure were reported different.

Design: Experimental population-based study

Setting: Urban areas, Isfahan city, Iran

Subjects: Nine hundred and twelve randomly selected patients aged 20-60 years

Main Outcome Measures: 24-hour urine and food records were collected three times in one month. Systolic (SBP) and diastolic (DBP) blood pressures, heart rate and sodium, potassium, calcium, chloride and creatinine levels in urine samples were measured.

Results: Estimated mean daily salt intake based on UNa excretion in Iranian population is 9.9 ± 2.9 g/day (men: 11.1 ± 3.0 g/day and women: 9.6 ± 2.9 g/day; p = 0.001). The UNa excretion value was 189.7 ± 51.4 mmol for men and 164.6 ± 49.8 mmol for women, with a significant difference (p = 0.001). After adjustment for confounding factors and other urinary electrolytes, no relationship was found between UNa and SBP (b = 0.001, p = 0.89) or DBP (b = 0.007, p = 0.34) in the pooled data. Significant relationship was observed between UCl excretion and SBP in hypertensives (b = 0.113, p = 0.001), UNa excretion and DBP in the entire group (r = 0.04, p = 0.004) and in normotensive men (r = 0.036, p = 0.03).

Conclusion: Salt intake is one of the main factors affecting blood pressure among Iranian men but not women.

KEY WORDS: blood pressure, chloride, electrolyte, hypertension, Iran, salt, sodium

INTRODUCTION

Hypertension is one of the major risk factors for cardiovascular disease (CVD) contributing to myocardial infarction, cerebrovascular events, congestive heart failure, peripheral arterial insufficiency, and premature mortality[1].

Some variables like diet have been identified as determinants of blood pressure. Among dietary factors, salt is an important modifiable determinant[2]. Evidence from animal and epidemiological investigations point to a direct association between excessive salt intake and stroke mortality, independent of blood pressure[3]. Data from the INTERSALT study have strengthened the epidemiological evidence indicating an association between dietary salt intake and blood pressure in western societies[4]. In addition, it has been found that hypertension is less prevalent in the primitive populations with a low salt and high potassium diet compared to western societies with high salt intakes[5].

In an animal study, it was found that a high sodium chloride diet causes significant hypertension, whereas an identical sodium load as a bicarbonate salt or other sodium salts, produces no significant effect compared to control animals with usual sodium chloride intakes[6]. In contrast, several studies did not report a direct effect of salt on blood pressure[7]. Therefore, dietary intervention may have an important role in blood pressure alleviation.

Due to the high prevalence of hypertension in Iran and Isfahan[8], we decided to investigate the relationship between 24-hr urinary sodium, as a measure of salt ingestion as well as chloride excretion and blood pressure level among an urban sample in Iran.

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SUBJECTS AND METHODS

This population-based study was conducted in 2001 with 912 people living in Isfahan aged 20-60 years (304 men, 608 women). Sampling was done equally in the four seasons from 40 randomly selected clusters. The original sample was 1010 and the participation rate was 90%. This study was approved by the local ethical committee and informed consent was obtained from the patients. Patients with renal disorders such as nephrotic syndrome and renal failure, heart failure, diuretic medication, diarrhea and hemorrhage were excluded from the study and were replaced with their neighbors in the same age group, body mass index (BMI) range and educational and socio-economical status. The subjects who had not collected the 24-hr urine samples were excluded from the analyses (n = 98). The excluded samples were similar to the total participants in the field of BMI, hypertension prevalence, and some other variables. Therefore, only 912 participants (652 normotensives and 260 hypertensives) were included in this analysis.

The methods used to carry out this study were obtained from INTERSALT study[9]. Through a home interview, information was obtained by a questionnaire on personal and anthropometric characteristics and CVD risk factors profile, etc. Each participant was trained to record all food consumption during a 24 hour-period. Also, the subjects were asked to collect all the urine excreted during the period in special jars. The interviewers gave participants the required instruction for accurate urine collection. The starting time for urine collection was immediately after voiding the spot urine sample. The value of creatinine excretion was measured as a marker of completeness of 24-hr urine collection (in adults under the age of 50, daily creatinine excretion should be about 20 to 25 mg/kg lean body weight in men and 15 to 20 mg/kg in women. From the ages of 50 to 90, there is a progressive 50 percent reduction in creatinine excretion (to about 10 mg/kg in men)[10].

This process was repeated three times in a month for each subject.

Height and weight of all subjects were measured by Seca scale in light clothes and without shoes. Blood pressure was measured after at least 30 minutes, during which the subjects did not eat, drink or smoke (only water was allowed) with a sphygmomanometer. Blood pressure measurements were performed after five minutes of rest by two well trained nurses following standardized procedure for blood pressure measurement described in INTERSALT protocol[9]. These measurements were carried out twice in the sitting position from the right arm, and the mean value of the two measurements was used in this study. Hypertension was defined as SBP > 140 mmHg and/or DBP > 90 mmHg or using antihypertensive medication. Heart rate was measured after measuring blood pressure.

As the urine jars were labeled, the total volume of urine was accurately obtained for each subject. On receipt of the urine samples, chemical analysis was immediately begun in the laboratory. Urinary sodium, potassium, calcium and chloride were determined by flame photometry. Creatinine was measured as a determinant indicating samples as 24-hour ones by Jaffe method (Technical SMA 12-60). For quality control, in addition to checking our results against standard urine and standardizing our laboratory with the Reference Laboratory in Tehran, the validity of laboratory urinary tests was confirmed by the INTERSALT Central Laboratory in Leuven, Belgium.

**Statistical analysis**

The SPSS software was used for the statistical analysis of the data. For comparison of mean values between men and women the student’s t test was
used, while multiple linear regression was done to determine probable relationship between urinary electrolytes and blood pressure.

RESULTS

The estimated dietary sodium chloride intake (according to 24hr urinary sodium excretion) is nearly 9.9 ± 2.9 g per day for the 20-60 year Isfahan population.

Table 1 shows the basic characteristics of the study population. The mean values of 24-hr urinary calcium and potassium excretion were 116.1 ± 52.8 mg/day and 56.9 ± 19.8 mmol/24-hr in men, and 102.7 ± 44.2 mg/day and 56.7 ± 21.8 mmol/24-hr in women, respectively. Also, urine creatinine level was 18.7 ± 5.7 and 15.9 ± 3.0 mg/24-hr/kg lean weight for men and women, respectively.

The mean values of sodium chloride intake was 9.9 ± 2.9 g/day and for sodium excretion 169.9 ± 50.4 mmol/24-hr which were significantly different between men and women (p = 0.001, Table 2).

According to Table 3, among the factors that can affect blood pressure (age, sex, body mass index (BMI), education, and physical activity), BMI, age and education had statistically significant associations with both systolic and diastolic blood pressures while physical activity was associated only with diastolic blood pressure (results for each sex are not shown). No relationship was observed for oral contraceptive use in women (not shown).

The association between 24-hr urinary sodium and chloride excretion, and systolic and diastolic blood pressure is shown in Table 4. After adjustment for the mentioned factors, neither of the electrolytes showed a significant relationship with systolic blood pressure [(sodium: b = 0.001, 95% CI: 0.019, 0.021), (chloride: b = 0.012, 95% CI: 0.013, 0.038)]. The same results were obtained for diastolic blood pressure. When the analysis was repeated for hypertensive and normotensive subjects, only chloride showed effect on systolic blood pressure in hypertensive group (b= 0.113, p = 0.001).

When multiple regression analysis including age, BMI and sodium, potassium, calcium and creatinine and heart rate were performed for both sexes separately, a significant positive relationship was observed between 24hr sodium excretion and diastolic blood pressure in the entire group (r = 0.049, p = 0.004) and normotensive men (r = 0.036, p = 0.030, not shown in the tables).

Also the relationship between sodium excretion and blood pressure were studied in hypertensive subjects without antihypertensive medication, and no association was obtained (systolic blood pressure: b = 0.010, p = 0.89; diastolic blood pressure: b = 0.092, p = 0.12).

DISCUSSION

A better estimate of habitual electrolyte intake would have been obtained from multiple 24-hr collections. Though this loss of precision in our study has in part been overcome by the large number of subjects, misclassification coefficient observed by us is likely to be attenuated as in other studies[5].

In Isfahan population, the mean salt intake (based on 24hr urinary sodium excretion) is similar to that of the non-primitives. The favorite
flavor in the Persian traditional foods is a salty flavor and our population is accustomed to salty foods. Also cheese is the most popular source of sodium in our population. High prevalence (28%) of systemic hypertension was reported in our society. Based on this evidence, the early hypothesis of salt having a role in increasing blood pressure in our society was proposed. High plasma sodium concentrations cause an increase in the osmotic pressure leading to an increase in the volume of the extra cellular fluid in vessels, which will ultimately result in a high blood pressure. Some authors believe that excessive dietary sodium is intimately involved in the pathogenesis of primary hypertension, playing a necessary but not sufficient role, while others do not agree.

In this study, no significant relationship or correlation was observed between the 24-hr urinary sodium excretion (as a measure of habitual dietary salt intake) and systolic or diastolic blood pressure. However, sex treated separately showed a positive significant association between 24-hr urinary sodium and diastolic blood pressure in the whole group and normotensive men. The INTERSALT, a worldwide study of salt intake and blood pressure achieved a positive relationship between 24-hr urinary sodium excretion and blood pressure at 52 centers. Over 70 published studies have addressed the impact of reducing sodium (salt) intake on blood pressure. Two large review articles have concluded that there is a linear relationship between sodium intake and blood pressure in different populations with different levels of sodium intake. Pan et al conducted a study in the Chinese community living in Taipei and reported a positive relationship between salt intake and blood pressure.

In contrast, many researchers could not find any significant association. For instance, a meta-analysis of randomized controlled trials did not recommend universal dietary sodium (salt) restriction for normotensive people. Furthermore, some researchers believe that the effect of sodium chloride on blood pressure is in fact related to its chloride content, so that other salts of sodium, such as sodium bicarbonate do not have a hypertensive effect. In the Chinese population living in Taipei, it was found that urinary chloride is positively associated with blood pressure. However, the present survey showed that urinary chloride ion excretion was not related to blood pressure (Table 4).

Based on the findings of this study, it is concluded that, firstly, the habitual dietary salt intake is high in our society. Secondly, salt or sodium intakes have an effective role on changing blood pressure of men in Isfahan. Thirdly, there is no relationship between sodium intake and blood pressure in women in Isfahan and it seems that high prevalence of hypertension in this group is related to other factors.

Nutrients occur in clusters in the typical human diet and may therefore act synergistically to alter physiological variables such as blood pressure. Dietary fiber has a role in blood pressure regulation but with inadequate consumption in our population. Recently a research in Isfahan showed that the mean intake of fiber is significantly more in subjects with high daily salt intake (≥ 6 g) than the others (< 6 g). Unfortunately, we could not find fiber intake in order to eliminate its interaction with dietary salt that may be considered a limitation. In addition to these factors, we must refer to limited power due to the narrow range of

<p>| Table 4: Association between urinary sodium excretion (as an estimate of daily salt intake) and systolic (SBP) and diastolic (DBP) blood pressures in hypertensive and normotensive subjects |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Systolic blood pressure | Diastolic blood pressure |</p>
<table>
<thead>
<tr>
<th></th>
<th>b (SE)</th>
<th>95%CI</th>
<th>p-value</th>
<th>b (SE)</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>0.001 (0.010)</td>
<td>-0.019,0.021</td>
<td>0.89</td>
<td>0.007 (0.007)</td>
<td>-0.007,0.020</td>
<td>0.34</td>
</tr>
<tr>
<td>Cl</td>
<td>0.012 (0.013)</td>
<td>-0.013,0.038</td>
<td>0.34</td>
<td>-0.007 (0.009)</td>
<td>-0.025,0.011</td>
<td>0.44</td>
</tr>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>-9.77E-04 (0.007)</td>
<td>-0.015,0.013</td>
<td>0.89</td>
<td>-0.009 (0.006)</td>
<td>-0.003,0.22</td>
<td>0.13</td>
</tr>
<tr>
<td>Cl</td>
<td>-0.003 (0.008)</td>
<td>-0.019,0.013</td>
<td>0.70</td>
<td>0.007 (0.007)</td>
<td>-0.007,0.021</td>
<td>0.34</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na</td>
<td>-0.005 (0.018)</td>
<td>-0.040,0.031</td>
<td>0.79</td>
<td>-0.007 (0.011)</td>
<td>-0.029,0.014</td>
<td>0.48</td>
</tr>
<tr>
<td>Cl</td>
<td>0.113 (0.030)</td>
<td>0.053,0.174</td>
<td>0.00</td>
<td>-0.026 (0.019)</td>
<td>-0.063,0.011</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Na: Sodium, Cl: Chloride, b: regression coefficient, SE = standard error
salt intake in our population.

Due to a wide range of individual reactions to low- and high-sodium diets, it might not be prudent to make the same dietary suggestions for everyone, as many researchers believe that salt consumption must be limited in both hypertensives and normotensives.[22] Also there is no sufficient evidence yet that low salt intake is a preventive factor for hypertension in normotensive people.[23]

Since coronary artery disease and stroke mortality rates have increased by nearly 18% since 1981 in Isfahan[24] and there is a positive relationship between salt intake and blood pressure in men in Isfahan, the Iranian population is advised to reduce its salt consumption.

ACKNOWLEDGMENTS

We wish to appreciate Prof. H Kesteloot for supporting our study as regards the quality control of the urinary tests of this survey. We also acknowledge the interest and support of our colleagues in the Isfahan Cardiovascular Research Center, especially, Ms I Gholshadi, N Abdar, R Vakili, M Moosavi, M Yarahgi and Mr. H Samarian.

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Original Article

Internet and Computer Use by Medical Students in Traditional and Problem Based Learning Systems

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ABSTRACT

Objectives: To validate the hypothesis that to achieve self-directed learning targets, medical students in Problem-Based Learning (PBL) curriculum would have higher levels of computer literacy and make greater use of the Internet compared to their counterparts in a traditional curriculum
Design: A questionnaire based study
Setting: Arabian Gulf University (AGU), Manama, Bahrain and the Medical School, University of Udine, Italy, during the academic year 2003-2004
Subjects: Years 2-4 medical students of AGU (PBL curriculum) and Year-3 medical students of MSU (traditional curriculum)
Main Outcome Measures: Comparison of computer ownership and literacy, and Internet usage among students in PBL and traditional curricula
Results: There was a high degree of computer literacy and ownership in both settings. The number of PBL students using word processing software was significantly higher (AGU 70.9% vs. MSU 34.7%; p < 0.05). The commonest Internet use was e-mail to chat with friends (> 90% in both institutions). Majority of the students obtained up to 40% of learning information online (MSU 93.9% vs. AGU 74.2%; p < 0.01). There was a significant increase from year 2 - 4 in the number of AGU undergraduates getting 40-60% of learning information online (p < 0.01). Access to original scientific literature as evidenced by websites visited and usage of Adobe Acrobat Reader® was lower among PBL students (MSU 51% vs. AGU 23.2%; p < 0.05).
Conclusion: For appropriate utilization of IT as an enriching PBL tool, more careful planning, integration and adequate guidance of the students with emphasis on content is needed.

KEY WORDS: computer, Internet, medical education, problem-based learning

INTRODUCTION

The use of computers and the Internet has dramatically revolutionized the ease with which information can be accessed. In medical education, there have been several attempts to use the Internet in diverse ways, including teaching, delivery of educational materials, as a source of materials for research and for the conduct of examinations[1-6]. The medical field is dynamic with new discoveries, diagnostic methods and management protocols constantly emerging. Medical students need immediate access to this rapidly expanding information and while the Internet provides the gateway, the onus still rests on the teacher to direct the students to sites where reliable and current information can be accessed.

This explosion in biomedical knowledge has also resulted in a change in the delivery of medical education and the rapid shift from traditional educative approaches to a non-didactic problem-based philosophy seen in the 1990s perhaps represents a strategy by which both students and teachers can cope with and hopefully manage this ever-expanding arena of information[1,2,8]. In the lecture-based traditional teaching system students are passive recipients of information whereas in a Problem-Based Learning (PBL) curriculum they are active participants in the learning process with emphasis on self-directed learning[9-11]. In the PBL curriculum, students take responsibility for their own learning through small group discussions during which problems are identified and learning objectives generated[12,13]. The students are expected to use diverse learning resources to gather relevant information and literature and prepare these in a concise manner for group discussion.

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With such emphasis on information gathering and evaluation, the Internet therefore becomes a potential powerful learning resource for the student. It could therefore be hypothesized that, in order to achieve their self-directed learning targets, medical students in the PBL curriculum would be expected to have higher levels of information literacy and information technology as well as make greater use of the Internet compared to their counterparts in a traditional curriculum. Although there are reports evaluating Internet and computer usage among medical students who were either in a traditional or PBL curricula\[2;14-17\], there are no direct comparative studies of medical students in these two curricula, in terms of computer and information technology (IT) utilization. Therefore, in this study, we compare Internet and computer usage among students in two medical schools with different education methods (PBL Vs. traditional curricula).

**SUBJECTS AND METHODS**

**Study Setting**

The study was carried out during the academic year 2003-2004 at the Arabian Gulf University, Manama, Kingdom of Bahrain and the Medical School, University of Udine, Udine, Italy; two medical schools with history of collaboration. The Arabian Gulf University (AGU) was established in 1982 and has utilized the PBL curriculum since its inception. The medical curriculum is divided into a pre-medical phase (Year 1), a three year pre-clerkship phase (Year 2-4) and a two year clerkship phase (Year 5 & 6). In the three year pre-clerkship phase, the learning strategy is organized around integrated organ/system units and taught using a PBL approach. The students in the PBL curriculum were exposed to basic medical sciences (anatomy, biochemistry and physiology) as well as the laboratory and clinical sciences from Year 2 - 4. The student population comprises of nationals of the Gulf Cooperation Council (GCC) countries namely Saudi Arabia, Bahrain, Kuwait, Oman, Qatar and United Arab Emirates (UAE). There are 632 medical students in the College of Medicine and Medical sciences (CMMS) and only one third (33.1%) are male. The Medical School, University of Udine (MSU), was established in 1987 and uses a traditional lecture-based curriculum. The six-Year undergraduate medical program consists of a three year pre-clerkship phase and a three year clerkship phase. In the traditional curriculum the first two pre-clinical years were dedicated to the basic medical sciences while exposure to laboratory medicine and aspects of clinical medicine only started in Year 3. The medical school has 543 students (39.4% male and 60.6% female). During the study period, it was ranked number one in the Italian National Survey of University Performance and the survey scoring parameters included productivity, teaching, research, profile of Faculty and international collaborations\[18\].

**Study Subjects and Recruitment Procedures**

Pre-clerkship phase students comprising 279 (Year 2: n = 99; Year 3: n = 93 and Year 4: n = 87) at AGU and 75 Year 3 students at MSU were recruited for the study. The decision to include only the Year 3 students in MSU was an attempt to compare students who were to a large extent being exposed to similar learning contents.

Verbal consent was obtained from all participants after informing them that participation was entirely voluntary, completely anonymous and was solely for research purpose without any bearing on their assessment. The questionnaire was distributed during a routine laboratory session; the students were given 20 minutes to complete it, and were requested to submit the finished questionnaires before leaving the laboratory.

**Questionnaire Design**

The pre-tested, anonymous questionnaire, comprising of 19 closed ended items, organized in sections related to formal training in computer use, ownership of laptop or personal / desktop computers (PC), types of software utilized, use of e-mail communication for personal or learning purposes, search engines utilized and websites visited. Questions related to frequency of utilization were rated using a Likert-type scale ranging from 1 “never”; 2 = not every week; 3 = once a week; 4 = more than once a week to “5 everyday”.

**Statistical analysis**

For clarity and consistency in the analysis, an acceptable threshold level of usage was set in advance. This acceptable threshold included: usage at least once a week for Word processing, web surfing and e-mail programs, and usage at least once a month for presentation, database software and Adobe Acrobat Reader®.

The data were entered in Microsoft Excel® and analyzed using SPSS version 12 statistical package. Statistical significance was calculated using Chi squared test.

**RESULTS**

**Student responses**

Out of 279 questionnaires distributed to AGU students, 155 (55.5%) were returned and analyzed. This comprised of 56/99 (56.6%) for Year 2, 36/93 (38.7%) for Year 3 and 63/87 (72.4 %) for Year 4.
At MSU there were 49 (65.3%) respondents. The proportion of female students in the study group was comparable in both settings (63.6% at AGU Vs. 58.6% at MSU).

**Formal computer training**

The majority of AGU students (83.2%) had received formal training in computer use compared to 61.2% at MSU (p = 0.049). In addition, the data indicates that AGU students received formal computer training earlier in their educational curriculum (71.3% at high school; Fig. 1A). However, at MSU, the university appears to play a major role in this respect as 73.3% received formal computer training in the Medical school. It is interesting to note that in both settings about 16% students utilized private sector tutoring to obtain formal computer literacy.

**Computer ownership**

Level of computer ownerships in both settings was very high (100% in MSU and 84.5% in AGU). Ownership of PC was significantly higher at MSU, while laptop possession was significantly higher among AGU students (p < 0.001; Fig. 1B)

**Computer utilization**

The students were asked about their utilization of various computer software including those for word processing, power point presentation, databases and Internet applications such as e-mail, web surfing and Acrobat Reader®. Microsoft Office® was the dominant package utilized by the students in both settings. Usage of Microsoft Word® based on the acceptable predefined threshold was significantly higher among AGU undergraduates (110/155; 70.9%) than MSU students (17/49; 34.7%; p < 0.05). Although the usage of other software such
as Microsoft PowerPoint® and Microsoft Excel® was less than 50%, no difference was observed in the two settings (Fig. 1C).

Among the applications used on the Internet, Acrobat Reader® was the only software that showed a significant difference in utilization. On the basis of the predefined acceptable threshold, 51% of MSU students used Acrobat Reader® compared to 23.2% at AGU (p < 0.01)

**Purpose of Internet access**

The commonest utilization of the Internet was for e-mail in both settings (Fig. 2A). Over 90% of students in both institutions used the e-mail for social communication with friends while 46 AGU (30%) and 8 MSU (16.3%) students used this tool to communicate with their peers for educational purposes. Only 16 AGU (10.3%) and 8 MSU (16.3%) students used e-mail to communicate with their teachers.

To assess the use of Internet as a resource tool, the students were asked to quantify how much of their medical learning information was obtained online. Fig. 2B shows that in both settings majority of the students obtained up to 40% of medical learning information online (MSU 93.9% vs. AGU 74.2%; p < 0.01). Thus it appears that more students in a lecture-based system were obtaining up to 40% of learning material from the Internet. From Year 2 to Year 4, we observed an increase in the number of AGU undergraduates getting 40-60% of medical learning information online which was statistically significant (p < 0.01).

The most commonly used search engine was Google followed by Yahoo. Analysis of sites visited was grouped within four major headings: medical (sub-grouped as sites of scientific publications and sites of medical organizations / bodies), news, socio-political and leisure. The number of students accessing medical and leisure sites was significantly higher at MSU. For sites of scientific publications, The National Library of Medicine (NLM) PUBMed Medline was visited by 38 students (30 from MSU). Although the overall number of students from both institutions was very low, The World Health Organization (WHO) and National Institutes of Health (NIH) USA websites were the top medical organization sites visited (accessed by 9 and 2 students respectively).

**DISCUSSION**

The way technology impacts delivery of education and student learning has been categorized as the 3Cs: computation (the technology and its power), communication (Internet and e-mail) and collections (network databases)[19]. In this study, we have examined aspects of these 3Cs to determine whether differences in IT utilization exist among preclinical students in terms of the educational philosophy of their medical schools.

The rapid increase in the availability, affordability and power of computers describe computation which is the first element of the 3Cs. The high level of computer literacy and ownership among students in both settings is in keeping with this element. However, while most AGU students obtained formal computer training at high school level, the university was the main provider of computer literacy training for MSU undergraduates. In the European study (Survey of European Universities Skills in ICT of Students and Staff)[20], an average of 42% (range: 23-58%) of new university entrants stated high school as the main source of their computer literacy. This compares unfavorably with the 70% observed in our study for AGU students coming from six different GCC countries (Fig. 1A). This should serve as a stimulus to the European Union policy makers to actively support programs aimed at promoting computer training at high school level.

The availability of computer education as part of the academic curriculum does not appear to completely marginalize private sector input as up to 16% of students in each setting still received private tutoring. Various factors such as the desire for personalized tutoring, to focus on specific areas of deficiencies or enthusiasts wanting to gain in-depth knowledge may account for students seeking private tutoring in computer education. The high level of computer ownership seen in both settings (AGU 84.5%; MSU 100%) was comparable. This is similar to 74% in Jordan, 71.7% in Denmark but considerably higher than 56% in Malaysia, 26% in Nigeria and 8.9% reported in Turkey[16,17,21-23]. Laptops are getting smaller in both size and weight but bigger in computational capability thus making them extremely attractive (despite the higher cost) to people on the move or where space is at a premium. In addition to Bahrain, nationals from the other five GCC countries are represented in the AGU student population. For these highly mobile students who travel back to their home countries during weekends or holidays but live in hostel accommodation on campus, the laptop probably represents a convenient cost-effective alternative to the PC. Furthermore, the high level of affluence in the region can also explain the significantly higher number of laptop ownership among AGU students.

The self-directed learning philosophy of the PBL curriculum as applied at AGU[24,25] requires that students acquire, appraise and present information necessary for problem solving. The significantly high
utilization of Microsoft Word® among students in the PBL curriculum reflects the fact that this was the software of choice for the preparation of material for discussion at small group tutorials. Many scientific publications are available for download in Acrobat Reader® format which is more printer and reader friendly than the HTML format. Therefore, usage of this software was selected as an indirect measure of access to scientific publications. With the high premium placed on self acquisition of knowledge from diverse sources in PBL, it was surprising that the utilization of this software was significantly lower among AGU students. It is possible that AGU undergraduates were less familiar with Acrobat Reader® and therefore downloaded publications in the HTML format or have been using the software without paying attention to its commercial name. However, this scenario seems unlikely because analysis of questions about the specific websites visited confirmed that a significantly higher number of MSU students accessed scientific publications probably as a reflection of the research oriented faculty recommending original articles as reference material for the students.

The second element of the 3Cs is communication. Online communication with friends using e-mail was the commonest indication for Internet access by both AGU and MSU students. This is in keeping with findings from other studies[16,23,26-28] thus underscoring the universal human need to communicate[29]. The use of the Internet and e-mail as an information and communication channel has been successfully established in many universities[1,3,5,30]. The high degree of e-mail usage in both settings further supports the notion that educators should actively promote the integration of E-communication as an additional tool to enhance interactions of faculty and students[23].

Access to information represents the final element of the three Cs (collections). Medical information is now available on the web in readily searchable and retrievable formats. In both institutions majority of students obtained up to 40% of medical learning information online. While the number of AGU students who make greater use (40-60%) of the Internet increased from Year 2 to Year 4, we were unable to determine if MSU students also showed a similar pattern as only Year 3 students were included in the study. Nevertheless, it appears that the PBL students appreciated the huge potential of the Internet as a useful educational resource tool and therefore utilized it more as they progressed through the curriculum. This may also indicate their maturity in finding a proper balance among the various educational resources available. However, guidance by faculty as well as continued provision of training in search strategies would help to motivate the PBL students discover the usefulness of the Internet as a resource tool early in their medical training. Additionally, the input of the faculty to provide direction in the choice of websites visited and analysis of information obtained online remains crucial as this is a skill that would remain useful to the students in their future practice as doctors. We are currently following a cohort of students as they progress in their medical education to examine the changes that occur in their usage of the Internet as a resource for learning.

In this study students from two diverse cultural settings were compared, thus introducing potential confounding factors, which might influence the observed behaviors independent of the educational systems. However, the students’ behaviors demonstrated more similarities than differences suggesting that the contribution from these confounders is negligible, with the major diversity being the different educational system. However, even when the latter is considered the differences expected we see as educators were not apparent. This is in line with data suggesting evidence of absence[16,31-33] in aspects of students’ outcome when lecture-based and PBL curricula are compared.

Information technology represents a powerful tool which has the potential of enriching any learning experience. However, for its appropriate utilization in a PBL curriculum there is a call for a motivated faculty to place emphasis on the content available to the students rather than on the technology per se. By doing so the major educational goals of PBL represented by the interdisciplinary approach and self-directed inquiry will be preserved.

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Management of Unicameral Bone Cyst of Proximal Femur: Experience of 14 Cases and Review of Literature

Magdy M Abdel-Mota’al, Abdul Salam Othman Mohamad, Kenneth Chukwuka Katchy, Amarnath A Mallur, Fawzy Hamido Ahmad, Barakat El-Alfy


ABSTRACT

Objective: To assess the results of surgical treatment of unicameral bone cyst (UBC) involving the proximal femur

Design: Retrospective study of 14 cases of UBC of proximal femur

Setting: Al-Razi Orthopedic Hospital, Kuwait

Subjects and Methods: Fourteen cases of UBC seen and treated at Al-Razi hospital were included in the study. Their presentation and the method of treatment were recorded.

Intervention: Thirteen cases were treated surgically using intra-lesional excision (ILE). The cavity was filled with autogenous bone graft in three cases, hydroxyapatite matrix (HA) in eight cases, and combined autogenous graft and hydroxyapatite matrix in two cases. Internal fixation was carried out in six cases. External fixator was applied in one case from iliac bone to femur crossing the hip joint.

Main Outcome Measures: Patients were followed up post-operatively for an average period of 42 months (range = 9–120 months). They were observed for recurrence, complications and fracture healing.

Results: Recurrence was observed in one case while other cases showed healing of the cyst with consolidation and varying degrees of remodeling in one years time. A case developed mal-union and growth arrest with subsequent shortening. Avascular necrosis and coxa vara was detected in another case. All the fractures healed in the usual expected time according to age.

Conclusion: UBC of the proximal femur exhibits unique characters and complications. Hydroxyapatite matrix is a useful and effective bone substitute. Post-excision stabilization of the cyst is recommended to avoid mal-union and to facilitate post-operative rehabilitation and earlier return to normal activities.

KEYWORDS: pathologic fracture, proximal femur, UBC

INTRODUCTION

Unicameral bone cyst (UBC) is defined as an atrophic degenerative osteolytic process consisting of a cavity filled with fluid and lined by a membrane[1]. The membrane is composed of cells staining positively with CD68,SDF-1,STRO-1,RANKL and express RUNX2.UBC cells show 24.2% of apoptosis significantly higher than 17.2% of trabecular bone cells[2]. Biochemical analysis of the cyst fluid showed bone-resorptive factors, i.e., prostaglandins, interleukin 1 and proteolytic enzymes[3].

UBC has highest incidence between 5 and 15 years[1] and 50% of upper femoral lesion are over 17 and their age as high as 54 years[4]. It usually arises in the metaphysis of long bones immediately beneath the growth plate and the most common location is proximal humerus followed by proximal femur[1,4-7] which accounts for 27% of cases[5]. UBC was the underlying lesion in 40% of pathological femoral neck fractures in children[8]. Avascular necrosis (AVN) of proximal femoral epiphysis and collapse of the articular surface was reported as a complication of UBC involving proximal femur[9-11].

Among the wide range of different modalities described for treatment of UBC are: radical excision in form of subperiosteal partial diaphysectomy and allograft[12], subtotal resection with[13] and without bone graft[14], curettage and bone graft[6], multiple drill holes[15,16], intra-cystic prednisolone injection[5,9] and recently, intra-medullary flexible nails[17,18]. Some authors focused their interest on UBC and other benign lesions located at proximal femur as this area exhibits unique characters and complications[8,19-23]. The aim of this study is to describe our experience with the results of surgical treatment of UBC involving proximal femur in Kuwait.

SUBJECTS AND METHODS

The current study represents a retrospective
Table 1: Summary of the cases, presentation, treatment and their results

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at presentation</th>
<th>Sex</th>
<th>Side</th>
<th>Presentation</th>
<th>Work up</th>
<th>Location of the lesion</th>
<th>Location of the fracture</th>
<th>Displacement</th>
<th>Treatment</th>
<th>complications</th>
<th>Follow up months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>F</td>
<td>Lt</td>
<td>Pathological. fracture</td>
<td>C.T</td>
<td>Inter–subtrochanteric</td>
<td>Basotrochanteric</td>
<td>Displaced</td>
<td>ILE + local adjuvant + HA + DHS + Screw + Spica</td>
<td>Nil</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>M</td>
<td>Lt</td>
<td>Pathological. fracture</td>
<td></td>
<td>Intertrochanteric</td>
<td>Inter-trochanteric</td>
<td>Undisplaced</td>
<td>ILE + local adjuvant + HA + DHS</td>
<td>Nil</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>M</td>
<td>Lt</td>
<td>Pathological. fracture</td>
<td></td>
<td>Neck</td>
<td>Transcervical</td>
<td>Undisplaced</td>
<td>ILE + HA + KW’S + spica</td>
<td>Nil</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>M</td>
<td>Rt</td>
<td>Pain, limp, wasting of quadriceps</td>
<td>CT+ Bone scan</td>
<td>Head &amp; neck</td>
<td></td>
<td>-</td>
<td>ILE + Auto grafts + Ext fixator</td>
<td>Nil</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>M</td>
<td>Rt</td>
<td>Pain, limp, wasting of quadriceps</td>
<td>CT+ Bone scan</td>
<td>Intertrochanteric</td>
<td></td>
<td>-</td>
<td>ILE + local adjuvant + HA + Auto graft + DHS + Screw</td>
<td>Nil</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>F</td>
<td>Lt</td>
<td>Pain</td>
<td>C.T</td>
<td>Inter–subtrochanteric</td>
<td></td>
<td>-</td>
<td>Auto graft + DHS</td>
<td>Nil</td>
<td>120</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>M</td>
<td>Lt</td>
<td>Pain</td>
<td>C.T</td>
<td>Head &amp; neck</td>
<td></td>
<td>-</td>
<td>ILE + Auto grafts + Spica</td>
<td>Nil</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>M</td>
<td>Lt</td>
<td>Pain</td>
<td></td>
<td>Inter Trochanteric</td>
<td></td>
<td>-</td>
<td>ILE + HA + Auto grafts + spica</td>
<td>Recurrence</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>M</td>
<td>Rt</td>
<td>Pathological. fracture</td>
<td>-</td>
<td>Inter–subtrochanteric</td>
<td>Inter-trochanteric</td>
<td>Undisplaced</td>
<td>ILE + HA + spica</td>
<td>Nil</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>F</td>
<td>Rt</td>
<td>Pathological. fracture</td>
<td>-</td>
<td>Inter–subtrochanteric</td>
<td>Inter-trochanteric</td>
<td>Undisplaced</td>
<td>ILE + HA + spica</td>
<td>Nil</td>
<td>24</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>F</td>
<td>Rt</td>
<td>Pathological. fracture</td>
<td>-</td>
<td>Neck + Inter–subtrochanteric</td>
<td>Inter-trochanteric</td>
<td>Undisplaced</td>
<td>ILE + local adjuvant + HA + Spica</td>
<td>Shortening + mal union + growth arrest</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>M</td>
<td>Rt</td>
<td>Pain &amp; limitation of hip movements</td>
<td>-</td>
<td>Inter–subtrochanteric</td>
<td></td>
<td>-</td>
<td>ILE + local adjuvant + HA + Spica</td>
<td>Nil</td>
<td>33</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
<td>M</td>
<td>Rt</td>
<td>Pathological. fracture</td>
<td>C.T</td>
<td>Inter–subtrochanteric</td>
<td>Inter-trochanteric</td>
<td>Undisplaced</td>
<td>ILE + local adjuvant + HA + DHS</td>
<td>Nil</td>
<td>30</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>M</td>
<td>Rt</td>
<td>Pathological. fracture</td>
<td>-</td>
<td>Neck + inter–subtrochanteric</td>
<td>Neck</td>
<td>Displaced</td>
<td>Conservative</td>
<td>AVN, Coxa vara, shortening</td>
<td>85</td>
</tr>
</tbody>
</table>

Rt = Right, Lt = Left, ILE = Intra-lesional excision, HA = Hydroxyapatite, DHS = Dynamic hip screw, AVN = avascular necrosis, KW = Kirschner wire
analysis of 14 cases of UBC involving proximal femur treated at Al-Razi Orthopedic Hospital, Kuwait during the period from 1990 through 2003 (Table 1). Analysis was a thorough review of medical records, including medical history, clinical examination, work-up, operative details and follow-up at the clinic.

Age at presentation ranged from 5 - 30 years with an average of 13 years. Ten cases were male and four were female. All cases were symptomatic. Pathological fractures were the presenting symptoms in five cases. The other cases presented with pain, various degrees of limp, limited hip movement and quadriceps wasting. The right side was involved in eight cases. Radiographic examination was the basic imaging technique for all the cases, whereas CT was done for selected cases (case # 1, 4, 5, 6, 7 and 13) to assess bony destruction and bone scan for cases with doubtful diagnosis (case # 4 and 5).

In most cases the lesion was located in the intertrochanteric area with varying degrees of extension toward the neck and subtrochanteric region. The head and neck were involved in two cases (case # 4 and 7). The neck was affected in one case (case # 3). In one case (case # 14) diagnosis was based on typical X-ray appearance and clinical course[21,24]. In the other cases histopathological study of the curetted material confirmed the diagnosis.

Surgical treatment was employed in all cases with exception of one case (case # 14) which was referred from another hospital. The basic surgical technique in all cases was intra-lesional excision (ILE). Local adjuvant therapy was used in six cases (case # 1, 2, 5, 11, 12 and 13) which consisted of painting with phenol 40%, cleaning with alcohol 90% and irrigation with normal saline. The cavity was filled with autogenous bone graft in three cases (case # 4, 6, and 7), hydroxyapatite matrix (HA) in eight cases (case # 1, 2, 3, 9, 10, 11, 12, and 13) and combined autogenous graft and hydroxyapatite matrix in two cases (case # 5 and 8). Internal fixation was carried in the form of dynamic hip screw (DHS) in five cases (case # 1, 2, 5, 6 and 13) and KWs in one case (case # 3) which was removed in six weeks time. External fixator from the iliac bone to femur crossing the hip joint was applied in one case (case # 4).

RESULTS

Follow-up ranged from 9 -120 months with an average of 42 months. With exception of one case which showed recurrence 9 months after surgery (case # 8), the minimum follow-up was 24 months. All other cases showed healing of the cyst with consolidation and varying degrees of remodeling in one years time. The hardware was removed in three years time in three cases (case # 1, 6 and 13). Case # 11 developed mal-union and growth arrest of greater tuberosity growth plate with subsequent shortening. This required raising the heel and did not need any surgical procedure at the last clinical assessment. AVN and coxa vara were detected in another case (case # 14). She was 14 years old at last follow-up. Clinical evaluation showed fair range of movement with occasional hip pain. Radiographic examination reported incongruent congruity of the involved hip joint. She needs long follow-up to detect the onset of disabling degenerative changes which dictate reconstructive procedures. All the fractures healed in the usual expected time according to age.

DISCUSSION

The basic surgical technique employed in the current study was ILE in the form of curettage and cleaning of the wall by power burr. In order to improve the margin and to decrease recurrence rate, local adjuvant therapy was applied earlier through this study in six cases (case # 1, 2, 5, 11, 12, and 13). 40% phenol was applied with a cotton tipped applicator and was removed by lavage with alcohol[25]. No recurrence was reported in those cases. Phenol was first applied to UBC by Neer et al in 1966[6]. However, because of lack of recent evidence supporting the use of phenol in UBC, we did not use it in later cases.

We used autogenic bone graft alone to fill resultant cavity in three cases (case # 4, 6, 7). Neer et al reported surgical treatment of 129 cases of UBC by curettage (ILE) and bone graft. They evaluated 24 out of 31 cases located in the proximal femur and reported recurrence in four cases (17%). The results of allograft were compared to autograft used to fill the defect after curettage of 93 cysts located in proximal femur and humerus. In 35 cases treated with autograft, 21 cases (60%) were excellent, six cases (17%) showed residual defect and eight cases (23%) required re-operation. In 58 cases treated with allograft; 28 cases (48%) were excellent, 12 cases (48%) showed residual defect, and 18 (31%) cases required re-operation. Thus autograft was slightly better[26] and therefore indicated in recurrence, when there is a sufficient quantity of bone which can be conveniently taken to fill the defect[26]. Allograft is indicated for the pediatric age group with large cyst[4]. Campanacci et al did not find any relation between type of bone graft and rate of recurrence and pointed out the importance of packing of the cyst well as residual empty spaces might be a source for recurrence[5].

HA was reported to have been used to fill the cavity of benign bone tumor and lesions after surgical excision. Out of 22 cases of UBC treated
by curettage followed by packing of the cavity with high-porosity HA, complete healing without cyst recurrence occurred in 18 (78%) cases. New bone surrounding HA was radiologically detected within an average of 2.3 months. In the current study HA matrix was used alone to fill the curetted cavity in eight cases and combined with autogenic bone in two cases. All ten cases healed and showed varying degrees of remodeling without recurrence (Fig. 1a, b, and c).

Recurrence was reported in one case (7%) in the current study (case # 8). A 5-year-old boy presented with UBC involving the inter-trochanteric region of left femur. He was treated by ILE and packing of the cyst cavity with a mixture of HA matrix and autogenous bone graft. Early signs of recurrence were detected by the ninth month. It was reported that recurrence following surgical treatment was more frequent in patients under the age of 10 years, and age was a more reliable prognostic factor than the proximity of the cyst to growth plate.

In 1974, Scaglietti et al described minimally invasive empiric injection of UBC with methylprednisolone. He reported 72 cases out of which 11 were located in the proximal femur with a healing rate of 96%. Capana et al reviewed 90 cases of UBC treated by intra-cystic injection of methylprednisolone out of which 20 were located at proximal femur. He reported 80% satisfactory results and there was a need for two to six injections per patient in order to achieve healing. Recurrence after cyst consolidation was observed in 12 patients (13%). Pathological fracture developed in seven patients during the course of treatment. One of them was a displaced fracture at proximal femur four months after the onset of treatment which required open reduction and internal fixation. A limb-length discrepancy was observed in two cases without prior surgery or pathological fracture. One of them was at the proximal femur.

Campanacci et al compared 178 cases of UBC treated by curettage and bone graft to 141 cases treated by methylprednisolone injection. The recurrence rate was 33 and 15% respectively. Pathological fracture developed in two cases during injection treatment and in another 11 cases after recurrence of the cyst. AVN of the femoral head was observed in one case treated by injection therapy. It was found that healing response to intra-lesional corticosteroid injection is unpredictable and usually incomplete even after multiple injections. The failure rate in the weight-bearing bone is high.

Percutaneous injection of autogenous bone marrow was described for treatment of UBC. The results of single injection of bone marrow into UBC were reported in eight cases, four out of them in the proximal femur. Healing according to Capanna criteria was complete in one case, incomplete in six cases, no response in one case and there was no recurrence. In a series of 79 consecutive patients with UBC, the results of aspiration and bone marrow injection were compared with those of aspiration and injection of steroids. The author reported that no advantage could be shown for the use of marrow injection over steroid injection in treatment of UBC.

Autogenous bone marrow injection was combined with allogenic demineralized bone matrix for treatment of UBC in 23 patients five of them were in proximal femur. The average time for...
pain relief was five weeks, and the average time until patients returned to full unrestricted activity was six weeks. A second injection was required because of recurrence in five patients (22%) whereas pathological fracture occurred in one case\(^{30}\). Similar results were reported after injection of demineralized bone graft without bone marrow, suggesting that the use of bone marrow may not be necessary to achieve good results\(^{31}\).

Based on venous obstruction as a theory for development of UBC, Chigira \textit{et al} introduced the treatment by multiple drill holes. He reported on seven cases of UBC. Two were located in the femur. Healing was observed within six to eight months. One of the cysts located in the femur required curettage and bone graft because of poor healing\(^{15}\). The same technique was applied to 23 cases of UBC. Nine cysts were located in the femur. Recurrence was observed in 15 cases\(^{16}\).

Roposch \textit{et al} evaluated the results of flexible intra-medullary nail in the treatment of UBC in 32 cases. The cyst was located in the proximal femur in nine patients. Recurrence was observed after removal of the nail in two cases, one of which was located in proximal femur. Change of the nail was required in nine cases, three located in the femur. A varus deformity of proximal femur developed in five cases after consolidation of the cyst\(^{17}\). In series of 12 cases of UBC of proximal femur treated by flexible intra-medullary nail, complications were reported in three cases. Perforation of the nail through the lateral cortex led to coxa vara in one case. The nail was removed and the femoral neck was fixed with a plate. The nail was changed as it became too short for the growing child in two cases\(^{18}\).

In the current series there was a seven year old girl (case # 14) who presented with pathological neck fracture through UBC involving the femoral neck and inter-trochanteric area. She was treated conservatively in form of skin traction followed by hip spica. The fracture healed and the cyst consolidated, but she developed coxa vara and AVN of the femoral head (Fig. 2a, b, c). In a series of 20 children with pathological fracture of proximal femur treated conservatively, the fracture was displaced in eight cases. All of the displaced fractures healed but with coxa vara and AVN in one child, coxa vara in a second and coxa breva in a third child. All of 12 undisplaced fractures healed without deformity or avascular necrosis, but they required from 1 - 7 injections of prednisolone for healing of the cyst. Re-fracture was observed in six children 2 - 5 years after presentation\(^{21}\).

After pathological fracture through UBC the early radiological appearance suggests progressive healing of the cyst, but complete healing of the cyst seldom takes place without operative treatment\(^{22}\). Hence, the proximal femoral cyst needs to be surgically treated to avoid mal-union and persistence of the cyst\(^{19,33}\). Wai \textit{et al} reported 11 cases of pathological fractures of proximal femur secondary to benign lesion. All cases were treated with curettage, high speed burring and reconstruction using a mixture of allo- and autogenic graft, and a fixed angle implant. All fractures healed without local recurrence\(^{23}\).

Both location of the cyst and the amount of bone loss dictate whether fixation can stabilize the fracture and type of fixation best suited for this purpose. Based on remaining bone in the femoral neck beneath the growth plate, bone in the lateral proximal femur

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{Case # 14 shows pathological fracture treated conservatively}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Healing with coxa vara and AVN (AP view)}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image3.png}
\caption{Healing with coxa vara and AVN (lateral view)}
\end{figure}
(lateral buttress) and skeletal maturity, Dormans et al. classified pathological fracture of femoral neck in children into three types with six subtypes and described the best fixation for each type\cite{19}.

Case # 1 presented with displaced pathologic baso-trochanteric fracture. It was type II-B according to classification proposed by Dormans et al\cite{19}. Treatment was in form of ILE, local adjuvant therapy, and filling the cavity with HA. The fracture was stabilized by DHS and anti-rotation screw. The hardware was removed two years after surgery. At 47 month follow-up there was excellent function, healing of the fracture without deformity and complete consolidation of the cyst (Fig. 3a, b, c). DHS was also applied to stabilize the fracture after surgical treatment in two cases classified as sub-type III-B (case # 2 and 13). Case # 3 presented with undisplaced pathological fracture neck and was classified as II-A\cite{17}. The fracture was fixed after surgical treatment with multiple KWs supplemented with hip spica (Fig. 4a, b).

Case # 11 was a seven year old girl who presented with pathological fracture through UBC involving the neck, sub- and inter-trochanteric areas. After surgical treatment it was difficult to stabilize the fracture because there was not enough bone between the cyst and capital epiphysis and deficient lateral buttress (Fig. 5a, b, c). This case was classified as II-B\cite{19}. The cyst consolidated and the fracture healed but with mal-union, shortening and growth arrest of the greater trochanter.

Few studies were published to assess the fracture risk in cases of UBC. Kaelin et al. devised a cyst index to assess the risk for fracture and found that in femoral fracture the average index was 4.4 (SD = 0.75), the lowest index was 3.6 and there was no fracture in cysts with index lower than 3.5\cite{24}. Shih et al. defined the criteria for impending fracture secondary to UBC of proximal femur as 2.5 cm or larger lytic area in the upper femur, a lesion involving half of the femoral neck or more and expansile lesion with thin cortex and progressive deformity\cite{22}.

Jaffe et al. reported management of seven patients with benign lesion of the femoral head and neck. The diagnosis was fibrous dysplasia in four cases, aneurysmal bone cyst in two cases, and UBC in one case. Curettage and autogenous fibular strut graft in conjunction with a sliding hip screw were carried out in six cases. One case was treated by curettage and strut graft. The results were excellent...
in five cases, good in one case and fair in one case. AVN of the femoral head developed in a case with pathological neck fracture through aneurysmal bone cyst[20]. Shih et al treated 35 cases of benign lesion of the femoral neck and inter-trochanteric area and 11 out of them were UBC. The lesions were curetted, filled with cortical strut allo-graft and autogenic iliac cancellous graft and fixed with sliding hip screw. They reported excellent results[22].

In the present study six cases presented with hip pain without fracture. We tried to apply Dorman’s classification[19] for selection of fixation after surgical treatment. Type III-B matched two cases (case # 5 and 6) where DHS was applied. The femoral head was completely destroyed by the cyst in two cases (case # 4 and 7, Fig. 6a, b, Fig. 7a). This type was not included in Dorman’s classification and was difficult to fix. Case # 4 was stabilized by external fixator extending from the iliac bone to proximal femur crossing the hip joint (Fig. 7 b). The treatment
was designed to achieve healing of the cyst and to prevent collapse of the articular surface. Our clinical assessment at 24 months follow-up reported minimal pain and good range of movement. Radiographic examination showed consolidation of the cyst with mild narrowing of joint space (Fig. 7c). At that time no active intervention was indicated. However, when disability develops reconstructive procedures for the hip will be considered accordingly.

CONCLUSION

UBC of the proximal femur needs special consideration as it exhibits unique characteristics and complications. Each case should be evaluated individually. HA matrix is useful and effective bone substitute particularly in the pediatric age group where there is limited supply of autogenic bone graft. Post-excision stabilization of the cyst is recommended to avoid mal-union and to facilitate post-operative rehabilitation and earlier return to normal activities. Choice of internal fixation depends on the location of the cyst, amount of bone loss and skeletal maturity. The surgeon, the patient and parents should be worried about the possible complications.

REFERENCES

Steroids for Reducing Post-Tonsillectomy Morbidity

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ABSTRACT

Objective: To determine the effects of a single dose of dexamethasone on post-operative morbidity in patients undergoing tonsillectomy / adeno-tonsillectomy

Design: Prospective, randomized, placebo-controlled clinical trial

Setting: Al-Sabah and Zain Ear, Nose, Throat Hospital, Kuwait

Patients: Eighty patients (47 male and 33 female), aged between 5 and 18 years, undergoing tonsillectomy and/or adenoidectomy.

Intervention: Patients were randomized to receive a single dose of intravenous dexamethasone or placebo (saline)

Main Outcome Measures: Post-operative pain, nausea, vomiting and edema were the primary outcome measures. Fever, time taken to resume oral fluids, duration of hospital stay, frequency of re-admission, and time taken for complete healing of the tonsil bed were also compared between the two groups.

Results: Statistically significant differences were noted in pain scores, post-operative nausea and vomiting (PONV), tolerance to oral fluids, discharge from hospital, re-admission and wound healing between the two groups of patients. In this study, dexamethasone did not significantly exert any effect on fever in the first 24 hours in patients undergoing tonsillectomy.

Conclusion: A single intra-operative dose of dexamethasone is an effective and safe method for reducing post-operative morbidity in tonsillectomy / adeno-tonsillectomy patients.

KEY WORDS: dexamethasone, post-operative morbidity, tonsillectomy

INTRODUCTION

Tonsillectomy and adenoidectomy are commonly performed otolaryngological operations, accounting for up to 20% of all operations performed by otolaryngologists. Despite improvements in anesthetic and surgical techniques, post-tonsillectomy morbidity has continued to be a significant clinical concern[1].

Post-tonsillectomy pain can limit oral intake and prolong the hospital stay. Similarly, post operative nausea and vomiting (PONV) can in addition cause tension on the sutures, venous hypertension, hemorrhage and pulmonary aspiration[2].

Dexamethasone has been used successfully as an antiemetic for chemotherapy induced vomiting[3] and is also proved to have an anti-inflammatory effect[4]. Analgesic effect of steroids has also been observed in other fields of surgical specialties[5,6]. These combined anti-emetic and anti-inflammatory effects may decrease post-operative edema and subsequently may improve oral intake after tonsillectomy.

The results of various randomized studies on steroids in post-tonsillectomy morbidity have demonstrated conflicting results, with some showing a clinical benefit[7-11] and others no benefit[12,13].

The aim of this study was to investigate the efficacy of a single dose of dexamethasone (1 mg/kg IV) on controlling the post-tonsillectomy morbidity, mainly pain, nausea and vomiting, and edema, and its influence on other factors like fever, intolerance to oral fluids causing prolonged hospital stay, complications, re-admissions and the healing time.

SUBJECTS AND METHODS

With approval from the Institutional Review Board, informed consent was obtained from each patient / patient’s parent / legal guardian.

Eighty patients (47 male and 33 female) between the ages of five and 18 years, posted for tonsillectomy or adeno-tonsillectomy were included in this study; 42 patients (25 male and 17 female) received a single intravenous dose of dexamethasone (1 mg/kg) intra-operatively and 38 patients (22 male and 16 female) received 5 ml saline IV as placebo.

Exclusion criteria were patients with medical or coagulation disorders or those with a known contraindication to steroid use. All
these patients fulfilled the routine pre-operative protocol for tonsillectomy/adenotonsillectomy, including history, ENT examination, and laboratory work-up such as complete blood count, prothrombin time and partial thromboplastin time.

The random allocation of participants into control group or dexamethalone group was done in the following way. In the operation theatre, the first two patients of this study group were given dexamethalone and rest were given saline and on the next operation theatre, this was reversed, i.e., the first two patients received saline and rest received dexamethalone. All the participants were blinded to treatment allocations.

The anesthetic protocol was standardized and did not include any other prophylactic antiemetic drug. All patients underwent normal oro-tracheal intubation. The calculated dose of dexamethalone or 5 ml saline was randomly administered after induction of anesthesia. The surgical technique was standardized for all patients by using the dissection method.

Bleeders were ligated using ties. When indicated adenoids were removed (50 patients) using curettes. Hemostasis was achieved using packs or sutures and electrocautery was used only to treat persistently active bleeding sites. No antibiotic was used.

Each patient had the following post-operative regimen for analgesia and anti-emesis: Paracetamol elixir 1gm orally was given routinely every 6 hrs; Profinal (5 mg/kg) was given orally when patient complained of pain and metoclopramide 5 ml orally when required.

All patients were monitored in the hospital for at least 24 hrs and the stay was prolonged depending on the morbidity. Each patient was monitored post-operatively for the following events. Pain was assessed by the need of additional analgesic (Profinal) post-operatively, i.e., when the patient complained of pain, extra analgesic was given and recorded. Number of episodes of vomiting after 6 hrs following tonsillectomy were recorded. If patient had more than two episodes of vomiting, metoclopramide was given and recorded. Tolerance to intake of 400 ml of oral fluids after 8 hrs following tonsillectomy was recorded. Edema as visual impression of swelling and elongation of uvula and soft palate was noted at 6 hrs and 24 hrs post-operatively. Temperature was recorded 4th hourly for 24 hours. Temperature of > 37.5 °C was considered as fever.

Patients were discharged after 24 hrs if good oral intake was achieved and when they were free from complications like bleeding, fever, pain, dehydration etc. Those patients who re-attend with secondary post-tonsillectomy hemorrhage, dysphagia with progressive throat pain and fever were admitted.

All patients had a regular follow-up visit with the consultant on 7th, 10th, and 16th post-operative day and information like fever, bleeding, vomiting and oral intake were collected during these visits. Healing time of the tonsil beds with complete removal of slough was noted at follow-up visit.

Statistical analysis:
The difference in various variables between the study group and the control group were assessed using Chi-square test and Fisher’s exact test wherever appropriate and a p value < 0.05 was considered as significant.

RESULTS
Eighty patients between 5 and 18 yrs of age were randomized to receive dexamethalone (n = 42) or placebo (n = 38). Maximum dose of dexamethalone used was 16 mg. No adverse effect of this drug was reported in our study. There was no significant difference in gender between the two groups; the male: female ratio was 1:0.68 in the study group and 1:0.73 in the control group. Also, there was no significant difference in mean age between the two groups (Mean ± SD = 8.3 ± 2.79 in study group Vs 8.6 ± 3.24 in the control group). Hence the groups were well-matched and comparable.

Table 1 shows the various post-operative events compared and analysed between the two groups. On the day of the operation, only six patients out of the 42 in the steroid group needed an extra analgesic, whereas 18 of the 38 patients in the placebo group required additional analgesics even after 48 hrs (p = 0.001). The chance of developing post-tonsillectomy pain in those patients who receive dexamethalone compared to those who do not is 0.185 (95%CI = 0.063 - 0.542, Table 1). This implies a statistically significant relative decrease in post-operative pain on the day of operation for those patients who received dexamethalone.

Twenty-five patients in the placebo group had more than two episodes of vomiting after 6 hrs post-operatively compared to only two patients in the trial group (p < 0.001). The risk of developing post-tonsillectomy vomiting in the dexamethalone group is only 0.026 compared to the control group (95%CI = 0.005 - 0.125). This implies a significant decrease in PONV in the dexamethalone group (Table 1).

All patients receiving dexamethalone were able to tolerate 400 ml of oral fluids at 8 hrs following surgery where as, none of the patients receiving the placebo could tolerate oral fluids at 8 hrs post-operatively. Thus, dexamethalone significantly improves oral intake in post-tonsillectomy patients.
Table 1: Comparison of post-tonsillectomy morbidities in the two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>Study group</th>
<th>Odds ratio (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>18 (47.4)</td>
<td>6 (14.3)</td>
<td>0.185 (0.063 – 0.542)</td>
<td>0.001b</td>
</tr>
<tr>
<td>PONV</td>
<td>25 (65.8)</td>
<td>2 (4.8)</td>
<td>0.026 (0.005 – 0.125)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (21.1)</td>
<td>2 (4.8)</td>
<td>0.188 (0.037 – 0.948)</td>
<td>0.041b</td>
</tr>
<tr>
<td>Edema</td>
<td>29 (76.3)</td>
<td>8 (19.1)</td>
<td>0.073 (0.025 – 0.214)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Oral fluid intolerance</td>
<td>38 (100)</td>
<td>0 (0.0)</td>
<td>0 (0.000 – 0.002)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Delay in discharge</td>
<td>8 (21.1)</td>
<td>0 (0.0)</td>
<td>0 (0.000 – 0.360)</td>
<td>0.002c</td>
</tr>
<tr>
<td>Re-admission</td>
<td>7 (18.4)</td>
<td>0 (0.0)</td>
<td>0 (0.000 – 0.425)</td>
<td>0.004d</td>
</tr>
<tr>
<td>Delayed healing</td>
<td>38 (100)</td>
<td>4 (9.5)</td>
<td>0 (0.000 – 0.013)</td>
<td>&lt;0.001b</td>
</tr>
</tbody>
</table>

*p-values are generated by chi-square test; b Fisher’s exact test

The incidence of edema was significantly less in the study group (8 Vs 29 cases in the control group, p < 0.001), at the end of 24 hrs after surgery. The relative risk of developing edema in dexamethasone group is only 0.073 compared to control group (95%CI = 0.025-0.214) and this is highly significant (Table 1). On the day of surgery, fever was recorded only in two patients from the study group compared to eight patients in control group (p = 0.041). The chance of developing fever following tonsillectomy in those patients who receive steroids is 0.188 compared to the control group (95%CI = 0.037 - 0.948, Table 1).

All the patients receiving dexamethasone were fit for discharge after 24 hrs post-operatively, but eight patients in the placebo group had to prolong their hospital stay due to morbidities like pain and dysphagia (p = 0.002). Thus dexamethasone significantly promotes early discharge of post-tonsillectomy patients (Table 1).

None of the patients from the study group got re-admitted signifying nil complications, whereas seven patients of the placebo group were re-admitted (p = 0.004, Table 1). Three out of them had secondary hemorrhage and four patients had severe dysphagia and throat pain.

Thirty-three patients of study group completed healing with normal tonsil bed on seventh post-operative day (POD) whereas only 33 patients from the control group completed healing after the tenth POD. Since none in control group completed healing on seventh POD, steroids have significantly (p < 0.001) promoted healing in post-tonsillectomy patients (Table 1).

DISCUSSION

Tissue injury induced acute inflammation, nerve irritation and spasm of exposed pharyngeal muscle is known to play a role in the genesis of post-tonsillectomy pain. By inhibiting phospholipase enzyme, corticosteroids block both the cyclooxygenase and lipo-oxygenase pathway and thus prostaglandin production, thereby leading to pain relief.

Corticosteroids reduce the inflammation by inhibiting the early processes of the inflammatory response which include edema, fibrin deposition, capillary dilatation, migration of lymphocytes and phagocytic activity.[14]

Corticosteroids reduce edema, whether the cause of inflammation is infection, trauma or allergy,[15] and are used extensively in otolaryngology in managing airway compromise as a result of laryngotracheal bronchitis, epiglottitis, laryngeal trauma, allergic laryngeal edema, subglottic stenosis and adenotonsillar enlargement secondary to acute infection.[16]

When given intravenously before surgery, dexamethasone has been effective in reducing postoperative edema, pain and trismus in patients who have undergone extractions for impacted third molars.[17] Given this accumulated information, it seems reasonable that dexamethasone given before tonsillectomy would improve the patient’s postoperative course.

Oropharyngeal pain and irritation of gastric mucosa by swallowed blood are the main contributors for high incidence of PONV following tonsillectomy. Steroids exert anti-emetic activity via prostaglandin antagonism, release of endorphins and tryptophan depletion.[18]

Multiple studies have shown benefits with corticosteroids alone or as adjuvant for chemotherapy induced vomiting, gynecological surgeries, thyroidectomy and opioid induced vomiting.

Henzi et al.[19] did meta-analysis of 17 trials involving use of dexamethasone for prevention of PONV in surgical patients. The number needed to treat to prevent early and late vomiting compared with placebo in adults and children was 7.1 (95% CI 4.5 to 18) and 3.8 (2.9 to 5) respectively. They concluded that when there is a high risk of PONV, a single prophylactic dose of dexamethasone is antiemetic compared with placebo, without evidence of any clinically relevant toxicity in otherwise healthy patients. Late efficacy seems to be most pronounced.

Local infiltration of steroids and an oral four day course of steroids have shown promising results in tonsillectomy patients.[20-22] However the literature regarding the use of intravenous corticosteroids for tonsillectomy is conflicting. Most of the studies...
have either lacked the control group or are not standardized for the anesthetic as well as surgical technique. There are controversies about the type and dose of the corticosteroid, whether to use single or multiple doses and whether to use alone or as adjuvant to other drugs.

McKean et al. did a double-blind randomized controlled trial of intravenous steroid for adult tonsillectomy and concluded that a single dose of 10 mg of dexamethasone given intravenously, at induction of anesthesia for adult tonsillectomy significantly decreased the pain scores for the day of operation and the mean pain score for the week post-operatively was significantly reduced in these patients. In this study, there was no difference noted in the time to first ingestion of food and drink.

Steward et al. did a meta-analysis of randomized double-blind placebo controlled trials of a single dose of intravenous intra-operative steroid for pediatric patients who underwent tonsillectomy or adenotonsillectomy. Eight trials met their inclusion criteria. They concluded that routine use of steroids would prevent vomiting in one out of four children. In addition, it would result in earlier soft or solid diet intake. But, because of the missing data and varied outcome measures, pain could not be meaningfully analyzed as a distinct end point.

Goldman et al. did a meta-analysis of dexamethasone use with tonsillectomy and six articles met their inclusion criteria. They also concluded that one out of four children was prevented from vomiting with peri-operative dexamethasone. An additional benefit was earlier tolerance of a soft / regular diet, but low precision and heterogeneity among studies have precluded definitive conclusion.

Our main aim was to find the effect of steroids on reducing the post-tonsillectomy pain, edema, nausea and vomiting. Dexamethasone was selected because it has a long half-life of 36 to 48 hours with glucocorticoid activity. A single dose lacks side effect like gastritis, adrenal suppression etc., and also has a low cost.

In our study, we administered dexamethasone 1 mg/kg, subject to a maximum dose of 16 mg immediately after induction of anesthesia and the anesthetic and surgical techniques were standardized for tonsillectomy and/or adenoidectomy.

Regarding the dosage of dexamethasone, doses ranging from 0.15 mg/kg to 1 mg/kg with maximum doses ranging from 8 to 25 mg have been commonly used in children. In a large study involving 133 patients, Splinter and Roberts have used 0.15 mg/kg dexamethasone with good results.

All the patients in our study group were monitored in the hospital for 24 hours and all attended routine follow up on the 7th, 10th and 16th POD.

In our study, majority of dexamethasone treated patients did not require extra analgesia on the day of surgery. This also indicates prolonged analgesic effect of dexamethasone.

The over all incidence of PONV was significantly less in our study perhaps also due to avoidance of electrocautery. More severe pain and hence PONV are known to occur with electrocautery.

Pappas et al. showed decrease in incidence of PONV from 62% to 40% using 1 mg/kg dexamethasone for adenotonsillectomy. In our study, incidence of more than two episodes of vomiting, six hours after surgery reduced significantly in dexamethasone treated patients. Similarly at the end of 24 hours after surgery, incidence of edema of soft palate and uvula reduced significantly in the dexamethasone treated patients.

There was a significantly better quality of oral intake with dexamethasone, perhaps due to less pain and inflammation.

In a meta-analysis Steward et al. showed that children receiving dexamethasone were more likely to advance to a soft or solid diet on post-tonsillectomy day one (RR = 1.69; 95% CI; 1.02 – 2.79, p = 0.04). In our study, all patients receiving dexamethasone were able to tolerate 400 ml of oral fluids at eight hours following surgery and none of the saline group was able to tolerate oral fluids at eight hours following surgery.

Our study did not show that dexamethasone can be used to control fever in post-tonsillectomy patients (p = 0.062).

All the patients who received dexamethasone were fit for discharge after 24 hours post operatively perhaps due to reduced overall morbidity. Eight patients from the control group had to prolong their hospital stay due to various morbidities like pain, fever and edema.

Similarly none of the study group was re-admitted whereas seven patients from the control group were re-admitted (three patients with secondary hemorrhage and four patients with difficulty in swallowing and pain).

During the follow up visits, 90% of the dexamethasone group completed healing with normal tonsil bed on the 7th post operative day and 87% of the saline group completed healing after 10th POD.

CONCLUSION

Our results showed that the use of dexamethasone 1 mg/kg in patients undergoing tonsillectomy and/or adenoidectomy significantly decreases the incidence of PONV, pain, and edema of uvula and...
soft palate. It also improves oral intake, shortens duration of hospital stay, reduces incidence of re-admission, and promotes early healing of tonsil bed significantly. Moreover, this single dose of dexamethasone is a safe and inexpensive method for reducing morbidity in tonsillectomy. But in this study, dexamethasone did not appreciably influence the fever in post-tonsillectomy patients. Even though a bigger sample size can increase the statistical power of the study, from our study (with this sample size and standardized surgical and anesthetic techniques) we can conclude that the routine use of dexamethasone seems reasonable in reducing post-tonsillectomy morbidity.

REFERENCES

ABSTRACT

Objective: To study the effect of adherence to asthma management guidelines on the control of asthma symptoms and the results of peak expiratory flow rate (PEFR) in asthmatic patients

Design: Cross sectional study

Settings: Asthma clinic at Khalidiya Health Care Center

Subjects and methods: A convenience sample of 162 asthmatic Kuwaiti patients aged between four and 83 years were interviewed through a structured questionnaire.

Results: Out of 162 patients, 140 participants (86.4%) reported not using controller medication. One hundred and five participants (64.8%) fit in the category of uncontrolled asthma. Only 21 participants (13.0%) were on controller treatment prior to the study. All participants who were on controller treatment, got their prescription by a specialist. The difference between the two proportions was significant at $p < 0.001$. Of the 162 participants, only 28 cases (17.3%) did not require alteration of their management plan. The remaining 134 participants required changes to their original management plan either by adjusting the dose of their medication or adding controller medication in the form of separate or combined therapy. There was a significant improvement in the PEFR after applying the new management plan with median of actual PEFR 350 in comparison to 390 two weeks later, after applying the new management plan ($p < 0.001$).

Conclusion: Despite evidence that adherence to asthma management guideline improves outcome, general practitioners are reluctant to prescribe controller medication.

KEY WORDS: asthma, controller medication, general practitioners, guidelines

INTRODUCTION

Asthma is a severe and sometimes fatal and chronic disease affecting a large proportion of the population[1]. It represents a significant health risk and public health burden in the United States. According to data from the national health interview survey, 10.2 million adults in the United States had asthma in 1996. By 2000, that number had increased to 14.7 million[2].

Western Europe has some of the highest prevalence rates of asthma in the world. Among children, the regional average is 13.0%; in adults the prevalence is lower (8.4%)[3]. Furthermore, according to data from the population-based surveys there has been a 2 - 4% annual increase in asthma prevalence rates in most European countries over the past 15 years[4].

Data in Kuwait shows that 18% of the population suffers from asthma manifestation[5]. Kuwait is ranked 13th among 56 countries in the prevalence of symptoms of asthma in children[6].

The primary mechanism for combating this well recognized increase in the prevalence of asthma has been the development of guidelines to promote standardized methods of diagnosis and treatment[7]. In 1993 the National Heart, Lung and Blood Institute (NHLBI) and the World Health Organization convened a working group to develop a global strategy for asthma management and prevention which was subsequently published as the Global Initiative for Asthma (GINA)[8].

The aims of this study were to assess the effect of adherence to asthma management guidelines on the improvement of asthma symptoms and to investigate its impact on peak expiratory flow rate (PEFR) in asthmatic patients followed up in the asthma clinic of the primary healthcare center at Khalidiya.

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SUBJECTS AND METHODS

Khaldiya Healthcare Center is a family medicine clinic that serves a population of 13,000. By using the ministry of health computer registry system, we identified 1907 subjects registered as asthmatics. Out of these 1907 subjects 1343 are Kuwaiti citizens and 564 are expatriates. Only 364 are registered in the asthma clinic registry. This number is explained by the fact that many asthmatic patients seek help only during acute attack and are thus not registered in the asthma clinic registry. Also, the expatriate population has high rate of turn over.

In this cross-sectional study, data were collected through a face to face interview using a structured questionnaire. The questionnaire was tested on a sample of fifty patients and the questions were corrected accordingly. Informed consent was obtained from all participants. This study was approved by the ethical committee in the Ministry of Health.

The sample comprised all Kuwaiti adult patients and parents of children less than 18 years of age (n = 162) attending the asthma clinic at Khaldiya healthcare center for follow up during the period September to December 2004. Patients attending the clinic with acute asthma attacks were not included in the study.

During the initial interview the following data was sought; demographic items such as age, sex, occupation, level of education for adults and for parents of children less than 18 years of age. Height of patients was measured because it’s a required parameter for the assessment of the actual and expected PEFR. Expected PEFR and actual PEFR were measured following the technique provided by the GINA guidelines[5].

Participants were asked about their current medications, who prescribed them and whether they are compliant to those medications. Current symptoms were determined by asking about the number of days during the past 14 days with any asthma symptom (including cough, wheeze, shortness of breath, or limited activity) in order to minimize recall bias.

Patients were categorized as having persistent (uncontrolled) asthma if they were symptomatic on three or more days during the past 14 days, corresponding to the definition of persistent asthma (> one symptom-days / week - GINA Guidelines)[3].

We also considered patients already on controller medications as uncontrolled if they met the previously mentioned category. Participants were classified as uncontrolled if their actual PEFR was less than the expected PEFR by 20%. PEFR was measured by using a peak flow meter (PFM)[5]. The best of three successfully performed maneuvers was included in the study.

Table 1: Socio-demographic characteristics of participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>97</td>
<td>59.9</td>
</tr>
<tr>
<td>Female</td>
<td>65</td>
<td>40.1</td>
</tr>
<tr>
<td>Age (in years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - 9</td>
<td>43</td>
<td>26.5</td>
</tr>
<tr>
<td>10 - 17</td>
<td>37</td>
<td>22.8</td>
</tr>
<tr>
<td>18 - 29</td>
<td>9</td>
<td>5.6</td>
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<tr>
<td>30 - 39</td>
<td>17</td>
<td>34.6</td>
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<tr>
<td>≥ 40</td>
<td>56</td>
<td>34.5</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below high school</td>
<td>15</td>
<td>9.3</td>
</tr>
<tr>
<td>High school</td>
<td>81</td>
<td>50</td>
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<tr>
<td>University and above</td>
<td>66</td>
<td>40.7</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>80</td>
<td>49.4</td>
</tr>
<tr>
<td>Teacher</td>
<td>17</td>
<td>10.5</td>
</tr>
<tr>
<td>Employee</td>
<td>31</td>
<td>19.1</td>
</tr>
<tr>
<td>House wife</td>
<td>20</td>
<td>12.3</td>
</tr>
<tr>
<td>Others</td>
<td>14</td>
<td>8.6</td>
</tr>
</tbody>
</table>

All participants that were classified as uncontrolled were prescribed controller medication in the form of separate or combined inhaler. For those already on controller medications, the dose was adjusted. Written instructions on how and for how long to use, what major side effects to expect, the difference between controller and reliever medications were provided. Finally the importance of long term management plan and compliance to treatment was stressed.

Participants were seen two weeks later when their PEFR was measured and enquiry made about their symptoms.

Statistical analysis:

Data were analyzed using the statistical package for social science, SPSS and descriptive statistics including frequencies, mean, and standard deviation were used to describe the study findings. The association between two qualitative variables was performed using the chi square test.

The value of $p \leq 0.05$ was used as a cut off level for statistical significance.

The 95% confidence interval (CI) for proportions was calculated assuming a binomial distribution. Non-parametric Wilcoxon - paired rank test was used to test the significant difference between medians.

RESULTS

The socio-demographic characteristics of the 162 participants is shown in Table 1. There was a
The predominance of male subjects (male: female ratio was 3:2). The age of participants ranged from 4 – 83 years. The sample included 80 children (≤ 18 years of age) and 82 adults (>18 years of age). The majority of participants were high-school graduates (50%), most of those were students (49.4%). Seventy one percent patients reported that they were compliant to their treatment.

One hundred and forty cases (86.4%) did not use controller medication at the initial assessment of participants in our study, compared to 21 cases (13.0%) that were on controller medication (Fig. 1). All 21 cases that were on controller medication were provided with the medication by a specialist. The difference between the two proportions was significant at p < 0.0001. In the meantime 105 cases (64.8%) were in the category of uncontrolled asthma and were either prescribed controller medication or the dose of their medication was adjusted. This means that almost two thirds of study participants were under treated with controller medication.

The AIRE Study[1] provides direct evidence that despite the availability of effective therapies, asthma control is suboptimal for many of the current patients in Western Europe. Only 22 patients (13.6%) were on controller medication prior to our study despite the fact that 105 patients (64.8%) were in the category of uncontrolled asthma and were either prescribed controller medication or the dose of their medication was adjusted. This means that almost two thirds of study participants were under treated with controller medication.

In a previous study regarding under-use of controller medications in 2002, Finkelstien et al found that 72.9% of children with persistent asthma were under users of anti-inflammatory medications[6].
Under-use of controller medications in the presence of persistent symptoms was alarming. In another study about under-use of inhaled steroid therapy in elderly patients with asthma, Sin et al found that 40% of elderly patients did not receive inhaled steroid therapy within 90 days of discharge from their initial hospitalization from asthma. Patients > 80 years of age were at greater risk of not receiving inhaled steroid therapy compared to those 65 to 70 years of age[7]. These results are alarming since clinical guidelines, including those of the NHLBI[8], GINA[9] and the National Asthma Education and Prevention Program (NAEPP)[9] advocate use of inhaled corticosteroids as first-line therapy in asthma. It makes us conclude that many physicians still hesitate to use inhaled corticosteroids as first line therapy in asthma. Murphy and Neierengarten reached the same conclusion in their article entitled ‘New Strategies for the Diagnosis of Asthma’[12]. Furthermore several researches published since the release of the GINA guidelines indicate that in many countries patients with asthma are inadequately treated[10,11]. This conclusion is in agreement with Logerretta et al[12] who in their study about compliance with NAEPP guidelines found that adherence was poor. Only 54% of respondents reported use of inhaled steroids daily. In addition, they also concluded that asthma specialists provided more thorough care than primary care physicians in treating patients with asthma. This is in agreement with our results that all the 22 cases that were on controller medication prior to our study were provided with controller medication by a specialist. The finding that 134 participants required alteration to their current management plan and that 105 participants required the initiation of anti-inflammatory medication raises the issue of primary care physicians’ reluctance to use controller medications and their lack of adherence to asthma management guidelines. This is consistent with the conclusion of Leogorreta et al[12] that asthma specialists provided more thorough care than primary care physicians in treating patients with asthma. In the study by Sin et al they also found that elderly patients who receive their care from primary care physicians were at higher risk of not receiving inhaled steroids in comparison with those under the care of specialists[10]. Hartert et al in their study about underutilization of controller and rescue medications concluded that despite widespread promulgation of the NAEPP guidelines, providers caring for indigent older subjects with moderate to severe or potentially fatal asthma were not following these guidelines[13].

We found in our study that adherence to asthma management guidelines especially the GINA guidelines in initiating controller treatment and adjusting the dose for those who were already on controller medication if their PEFR was less than the expected by 20%, resulted in improvement of the median actual PEFR. The improvement was significant with \( p < 0.0001 \). This is consistent with the results of a one-year study of patients with moderate asthma conducted by Zuwallack and co-workers[14]. They reported significant improvement in FEV1, evening PEFR and asthma symptom score with inhaled fluticasone propionate compared with placebo. Similar results were reported by Haahrela and colleagues[15], who found that inhaled budesonide was significantly more effective than terbutaline alone in reducing symptoms of asthma and improving morning and evening PEFR.

The START study found that budesonide was associated with significant effects on measures of the lung function. It demonstrated a significant improvement in pre and post-bronchodilator FEV1 for patients treated with budesonide, compared to patients treated with placebo (2.24 and 1.48%, respectively; \( p < .0001 \))[16].

CONCLUSION

Adherence to asthma management guidelines improves the outcome of bronchial asthma patients. There is a substantial under-prescription of controller medication among patients attending our asthma clinic. This reflects the doctors’ lack of adherence to asthma management guidelines. Following asthma management guidelines resulted in significant improvement in the PEFR.

More than 15 years have passed since the GINA guidelines were first published and still asthma patients are alarmingly improperly treated despite the evidence of the effectiveness of inhaled steroids.

In order to improve asthma patient care we need to target the first line gate-keepers, i.e. the primary care physicians and study the reasons for their reluctance to use controller medication and their lack of adherence to asthma management guidelines.

REFERENCES

5. Global Initiative for Asthma (GINA): global strategy for


INTRODUCTION

The term pancytopenia denotes simultaneous reduction in all the formed elements of the blood i.e., erythrocytes, leukocytes and platelets. Pancytopenia is not a disease entity but a triad of findings that may arise from a number of disease processes[1]. Pancytopenia, therefore exists when hemoglobin level is below 13.5 g/dl in males or 11.5 g/dl in females, leukocyte count below 4 x 10^9/l and platelet count below 150 x 10^9/l[2]. A number of bone marrow disorders like aplastic anemia, myelodysplastic disorders, acute leukemias, myelosclerosis and infiltration of bone marrow by lymphoma, myeloma, carcinoma, hairy cell leukemia, infiltrative disorders like Gauchers’ disease, Niemman Pick disease, Lietterer Siwe disease may produce pancytopenia[1].

The presenting clinical symptoms are usually due to anemia, leukopenia and thrombocytopenia. Fatigue and weakness due to anemia, increased susceptibility to infections because of leukopenia and bleeding tendency due to thrombocytopenia are the usual presenting symptoms[2].

Fifty cases of pancytopenia diagnosed at Regional Institute of Medical Sciences (RIMS) hospital during a period of two years were analysed. The present study was carried out to find the different causes or disorders among the patients with pancytopenia and their clinical correlation.

SUBJECTS AND METHODS

The present study was conducted in the Department of Pathology, Hematology section, RIMS hospital, Imphal over a period of two years from November 1999 to October 2001. Approval of local ethical committee was obtained to conduct this study. A total of 50 patients who fulfilled the criteria for pancytopenia were taken up for the study. All the 50 cases were subjected to bone marrow aspiration and examination. Consent was taken from all patients. Inclusion criteria for analysis were hemoglobin concentration less than 10 g/dl, total leukocyte count less than 4 X 10^9/l and total platelet count less than 100 X 10^9/l. Bone marrow aspirations were done in all the cases. A detailed clinical history and physical examination

ABSTRACT

Objectives: To determine the etiology and clinical profile of pancytopenia in Manipur, India
Design: Prospective study
Setting: Department of Pathology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, a renowned referral hospital in north-east India
Subjects: Fifty cases of pancytopenia were examined in the department of Pathology, RIMS hospital, Imphal, Manipur,India, during a two year period from November 1999 to October 2001.
Interventions: Bone marrow aspiration and examination
Main Outcome Measures: Correlation between pancytopenia and clinico-hematological diagnosis

Results: Hypoplastic anemia was the commonest cause of pancytopenia (22%) followed by megaloblastic anemia and myelodysplastic syndrome (18% each). The other causes include subleukemic / aleukaemic leukemia (14%), iron deficiency anemia (8%), HIV infection (6%), congenital dyserythropoietic anemia (CDA, 4%), pyrexia of unknown origin (PUO) with hepatosplenomegaly (4%), congenital hepatic fibrosis (2%) and systemic lupus erythomatosus (SLE, 2%).

Conclusion: Rare causes of pancytopenia including iron deficiency anemia, HIV infection and CDA have to be kept in mind as possible disorders manifesting as pancytopenia.

KEY WORDS: hypoplastic anemia, myelodysplastic syndrome, pancytopenia

INTRODUCTION

The term pancytopenia denotes simultaneous reduction in all the formed elements of the blood i.e., erythrocytes, leukocytes and platelets. Pancytopenia is not a disease entity but a triad of findings that may arise from a number of disease processes[1]. Pancytopenia, therefore exists when hemoglobin level is below 13.5 g/dl in males or 11.5 g/dl in females, leukocyte count below 4 x 10^9/l and platelet count below 150 x 10^9/l[2]. A number of bone marrow disorders like aplastic anemia, myelodysplastic disorders, acute leukemias, myelosclerosis and infiltration of bone marrow by lymphoma, myeloma, carcinoma, hairy cell leukemia, infiltrative disorders like Gauchers’ disease, Niemman Pick disease, Lietterer Siwe disease may produce pancytopenia[1].
were also performed for each case. Clinical details regarding age, sex, exposure to chemicals or drugs, bone pain, fever, night sweats, malaise and weight loss were inquired. Physical examination was done to detect presence of hepatomegaly, splenomegaly, lymphadenopathy, sternal tenderness, gum hypertrophy and primary malignancy. Peripheral blood smears were examined for the presence of anisopoikilocytosis, circulating erythroblast, hypo or hypersegmented neutrophils, abnormal granulations in neutrophils, lymphocytosis and immature WBC. Reticulocyte count was also done for all cases. However, the cytogenetic studies were not done due to lack of facilities in our institution.

**RESULTS**

A total of 23,335 cases were received for hematological examination during the study period. Out of these, 50 cases (0.2%) showed features of pancytopenia. The male to female ratio in the study was 1.5:1. The age ranged from 3 to 80 years. Maximum number of cases was observed in the 21 to 40 years age group with a slight male preponderance.

The commonest cause of pancytopenia was found to be hypoplastic anemia (22%), followed by megaloblastic anemia and myelodysplastic syndrome (MDS) (Fig. 1) with 18% each. The other causes include subleukemic / aleukaemic leukemia (14%), iron deficiency anemia (8%), HIV infection (6%), congenital dyserythropoietic anemia (CDA, 4%), PUO with hepatosplenomegaly (4%), congenital hepatic fibrosis (2%) and systemic lupus erythomatosus (SLE 2%, Table 1). Splenomegaly was observed in one patient of MDS. The patient incidentally had chronic liver disease. Out of the 11 cases of hypoplastic anemia three cases had history of analgesic intake or some unknown medicine off and on. One patient gave history of jaundice and another presented with alcoholism. Hepato-splenomegaly was seen in six cases of megaloblastic anemia out of which one gave history of taking carbamazepine for seven years. Out of the seven cases of acute leukemia, four cases had hepatosplenomegaly and three cases had lymphadenopathy. The two cases of congenital dyserythropoietic anemia had symptoms of anemia and bleeding. Foetal hemoglobin (Hb F) was slightly increased in both cases and Ham’s acidified serum test was negative. The signs and symptoms of the various cases of pancytopenia are shown in Table 2. The age and etiology distribution is shown in Table 3.

Detailed peripheral blood smear examination done in all patients revealed microcytic hypochromic red blood cells in two cases of MDS and macrocytes with anisocytosis in one patient. All the other cases had normocytic and normochromic

<table>
<thead>
<tr>
<th>Hematological Diagnosis</th>
<th>n</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Hypoplastic anemia</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Myelodysplastic syndrome (MDS)</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Megaloblastic anemia</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Subleukemic leukemia</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>HIV infection</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Congenital dyserythropoietic anemia (CDA)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>PUO with hepatosplenomegaly</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Congenital Hepatic fibrosis with PH</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Squamous cell Ca (N.S)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SLE</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50</td>
<td>100</td>
</tr>
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**Table 2: Sign and symptoms of pancytopenia**

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Weakness</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>Fever</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Bleeding</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Hepatomegaly with splenomegaly</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Pain abdomen</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Palpitation</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Edema</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Difficulty in breathing</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Menorrhagia</td>
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<td>2</td>
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</table>
red blood cells. Lymphocytosis was noted among cases of hypoplastic anemia. Immature white blood cells were noted in five out of seven cases of acute leukemia and in all cases of MDS. Histoplasma capsulatum was present in the bone marrow of one case of HIV infected patient (Fig. 2).

**DISCUSSION**

The pathophysiology of aplastic/hypoplastic anemia is now believed to be immune mediated. The aberrant immune response may be triggered by viral infections, exposure to chemicals and drugs or endogenous antigens\[^{2}\]. The mechanism is similar to tissue specific organ destruction mediated by lymphocytes seen in diabetes, multiple sclerosis, uveitis and colitis\[^{3,4}\]. Incidence of aplastic/hypoplastic anemia as a cause of pancytopenia varies from 10 to 52.7\(^{\%}\)\[^{3}\]. In our study, aplastic/hypoplastic anemia was the predominant cause (22\% of pancytopenia similar to a study conducted by Kumar\[^{5}\] et al. The incidence of MDS as a cause of pancytopenia was 2\% in a study conducted by Khungar\[^{6}\] et al. In our study MDS was the cause in 18\% of the cases. The incidence of megaloblastic anemia as a cause of pancytopenia varies from 0.8 to 32.26\%\[^{7}\]. The incidence was 18\% in the present study. In seven out of nine cases of megaloblastic anemia, there was association with cirrhosis/alcoholism/abnormal liver function. One patient was on carbamazepine for the last seven years. Only one patient was a pure case of megaloblastic anemia that had no associated disease or exposure to medicine. In the present study chronic liver disease or cirrhosis seemed to be the main cause of megaloblastic bone marrow, most likely to be due to folate deficiency.

Aleukaemic leukemia was noted in seven cases (14\%) of pancytopenia. In the present study, four out of seven cases were of acute lymphoblastic leukemia and three were of acute myeloblastic leukemia. In about 25\% of the patients with acute leukemia the total white cell count at the onset is reduced, ranging from 1 to 4 \(10^9\)/l. Occasionally, blast cells may be present in very small numbers\[^{8}\]. The symptoms of early acute leukemia are quite varied\[^{9}\]. General weakness, fever and bleeding were the common symptoms in a few cases of acute leukemia included in the present study. Other symptoms like swelling of the face, ascites, backache, anorexia, headache and loss of consciousness were also observed in a few patients.

Congenital dyserythropoietic anemia (CDA) type-1 producing pancytopenia was seen in two cases (4\%) in the present study. The bone marrow showed features of dyserythropoiesis with normal leucopoiesis and megakaryopoiesis. CDA must be considered in the differential diagnosis of MDS especially in young patients\[^{10}\]. In the two cases, MDS had been ruled out by the presence of normal leucopoiesis and megakaryopoiesis. Maeda et al described a case of CDA type-1 developing pancytopenia possibly due to enlarged spleen\[^{11}\]. One case of CDA type-1 in the present study also had massively enlarged spleen and pancytopenia. Hypersplenism and splenic pooling may contribute to the pancytopenia. The other case had bone marrow hypoplasia along with features of dyserythropoiesis. Hypoplasia of the marrow may be the cause of pancytopenia. Patients infected

<table>
<thead>
<tr>
<th>Table 3: Age and etiology wise distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in yrs</strong></td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td>0-15</td>
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<tr>
<td>16-30</td>
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<td>31-45</td>
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<td>46-60</td>
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<tr>
<td>61-75</td>
</tr>
<tr>
<td>76-90</td>
</tr>
<tr>
<td>11-98</td>
</tr>
</tbody>
</table>

HA: Hemolytic anemia; MDS: Myelodysplastic syndrome; SLE: Systemic lupus erythematosus; PUO: Pyrexia of unknown origin; HIV: Human immunodeficiency virus; IDA: Iron deficiency anemia; CDA: Congenital dyserythropoietic anemia

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**Fig. 2:** Photomicrograph of bone marrow smear from an AIDS patient showing *Histoplasma capsulatum* in macrophage (Leishman’s stain, X1000)
with HIV had uni or multi lineage suppression of the bone marrow hematopoiesis along with decrease of CD4+ peripheral blood lymphocytes[12]. All the three patients with HIV in the present study had pancytopenia due to bone marrow suppression. Some patients with severe iron deficiency anemia or long standing iron deficiency may have mild thrombocytopenia possibly due to complicating factors like folate deficiency or splenic sequestration[13]. Mild granulocytopenia may occur in long standing cases of iron deficiency[14]. An association between severe iron deficiency and thrombocytopenia has been observed probably due to an essential role of iron in a late stage of thrombopoiesis[15]. Increase in platelet counts following packed red blood cells transfusion have been observed in some studies[16]. Anemia and associated neutropenia may be due to associated copper deficiency possibly because of the decrease activity of enzymes containing copper[17]. Four cases (8%) of iron deficiency anemia in the present study had prolonged bleeding. Pancytopenia with marrow failure had been observed in patients with malignant ovarian tumours[18]. One case of squamous cell carcinoma of the nasal septum without history of prior chemotherapy has been included in the present study. One case of congenital hepatic fibrosis with portal hypertension was also observed in the study. Hypersplenism may be the possible cause of pancytopenia. Malaria related cytopenia was noted in studies done by Cannard and Aouba et al[19,20]. One case of malaria was seen in the present study. In SLE pancytopenia occurs when there is simultaneous depression of erythrocytes, platelets and leukocytes. The bone marrow is usually cellular and rarely hypocellular[21]. One case of SLE was noted in the present study. Bone marrow was normocellular and peripheral blood smear showed pancytopeny. Among the pediatric age group, Bhatnagar et al observed acute leukemia (ALL, AML and MDS) and aplastic anemia in 21% and 20 % respectively, megaloblastic anemia in 31 (28.4%) patients and infections in 23 (21%) out of 109 patients presenting with pancytopenia. In our study, out of the 50 cases, there were eight pediatric cases. Acute leukemia and hypoplastic leukemia accounted for two cases each and one case (2%) each of megaloblastic anemia, infantile hepatic fibrosis with splenomegaly, CDA type -1 and squamous cell carcinoma[22].

CONCLUSION

In our study, pancytopenia has been observed in association with iron deficiency anemia, HIV infection, CDA and carcinomas (squamous cell carcinoma). It is necessary to be aware of these disorders manifesting as pancytopenia.

REFERENCES

Original Article

Genotype – Phenotype Correlation in 46, XY Females

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Division of Human Genetics, Department of Anatomy, St. John’s Medical College, Bangalore, India


ABSTRACT

Objective: XY females are phenotypically females, but with XY karyotype. Our aim was to correlate the genotype with phenotype in cytogenetically confirmed 46 XY females.

Design: Retrospective study of a thirty year data

Setting: Division of Human Genetics, St. John’s Medical College, Bangalore, India

Subjects: Six hundred and twenty consecutively referred individuals with primary amenorrhea

Main Outcome Measures: Phenotype features and XY female characteristics

Results: Fifty-seven (9.2%) cases were identified with 46, XY karyotype.

Primary features: Uterus was absent in 33/47 (70.2%) cases and gonads absent in 18/34 (52.9%). Complete female external genitalia was observed in 36/48 (75%), ambiguous genitalia with clitoromegaly in 12/57 (21.1%), normal vagina in 13/48 (27.1%), blind in 27 (56.3%) and absent in 8 (16.7%) cases.

Secondary features: Normal breast was seen in 23/54 (42.6%), hypoplastic in 16 (29.6%) and absent in 15 (27.8%) cases. Axillary and pubic hair was normal in 6 (11.1%) and poorly developed in 48 (88.9%). Twelve (85.8%) were born to consanguineous parents and 8 had first cousin relationship (66.7%). The highly significant features associated with consanguinity were normal axillary hair, ovotestis, absent vagina and significant features were hypoplastic / normal pubic hair, absent gonads and clitoromegaly.

The observed differences in the percentage calculation were because of the overlapping in features as well as the available information in the records.

Conclusions: Genotype and phenotype correlation revealed that in primary features, absence of mullerian derivatives and gonads were important whereas in secondary features, axillary and pubic hair was poorly developed.

KEY WORDS: 46 XY females, consanguinity, counseling, primary sexual characteristics, secondary sexual characteristics

INTRODUCTION

XY female condition is also known as Swyers syndrome/ XY gonadal dysgenesis/ XY sex reversal or male pseudohermaphroditism. Usually the clinical features are female phenotype, normal to tall stature, bilateral dysgenetic gonads and sexual infantilism with completely female external genitalia to ambiguous genitalia and primary amenorrhea (PA)[1,2].

There are three types of sex differentiation, namely, genetic sex established by the sex chromosomal constitution at the time of fertilization, gonadal sex involving the differentiation into testis or ovum depending on the genes located on sex chromosomes as well as autosomes and lastly the phenotypic sex, which differentiates to the hormonal response[3].

XY gonadal dysgenesis is considered to be a heterogeneous disorder because it may be X-linked recessive or Y-linked or male limited autosomal dominant[1].

In the present study, the genotype, the phenotype and the presence of consanguinity in individuals with PA having 46 XY karyotype is reported.

SUBJECTS AND METHODS

Six hundred and twenty individuals with PA were consecutively referred to the Division of Human Genetics, St. John’s Medical College, Bangalore, from 1973 to 2004 for karyotyping and counseling, from different states of India, mostly from the south.

For each referral, information in detail was obtained about the family history, clinical history and pedigree traced for three generations.

Chromosomal preparation: Working solution of medium was prepared by adding 16 ml of heat inactivated human AB serum to 80 ml of medium. Cultures were set up with eight drops of heparinised blood in culture vials containing 5 ml of medium and 150-200 ul/ml of PHA. Cultures were incubated at 37 °C, for 72 hours. On the second day, the caps
of the culture vials were slightly opened to allow air to enter the bottles. At 70 hours cultures were harvested and then, slides were prepared. The dried slides were treated with a solution of 1 ml 0.25% trypsin in 49 ml saline (30 secs). Then, they were stained in a solution containing 1 ml Giemsa stain, 1 ml phosphate buffer and 48 ml de-iodinised water. Slides were washed, dried and mounted. Fifteen metaphase spreads were analysed, three were drawn and photographed. This study was approved by the institute ethical committee.

### Table 1: Phenotypic features – 46 XY females

<table>
<thead>
<tr>
<th>Features (n)</th>
<th>Normal n (%)</th>
<th>Scanty/ Hypoplastic n (%)</th>
<th>Absent n (%)</th>
<th>Absent n (%)</th>
<th>One side absent n (%)</th>
<th>Testis/ Ovotestis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus (47)</td>
<td>1 (2.1)</td>
<td>13 (27.7)</td>
<td>33 (70.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gonads (34)</td>
<td>-</td>
<td>5 (14.7)</td>
<td>18 (52.9)</td>
<td>2 (5.9)</td>
<td>9 (17.6)</td>
<td>-</td>
</tr>
<tr>
<td>Axillary/pubic hair (54)</td>
<td>6 (11.1)</td>
<td>20 (37)</td>
<td>12 (22)</td>
<td>16 (29.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Breasts (54)</td>
<td>23 (42.6)</td>
<td>16 (29.6)</td>
<td>15 (27.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 2: Types of consanguinity - 46 XY females**

<table>
<thead>
<tr>
<th>Consanguinity (n = 14)</th>
<th>Uncle-niece n (%)</th>
<th>1st cousins n (%)</th>
<th>2nd cousins n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental (12 / 85.8)</td>
<td>3 (25)</td>
<td>8 (66.7)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Grand-parental (1 / 7.1)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maternal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paternal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Parental / Mat &amp; Pat grand parental (1 / 7.1)</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

### RESULTS

In the sample of 620 with PA, 57 (9.2%) were cytogenetically confirmed to be 46 XY females. It is to be noted that in all the 57, complete information could not be obtained. Hence, there exists the variation in the percentage calculation. Moreover, the features were overlapping. The mean height and standard deviation for the 54 cases of 46 XY females was 156.04 ± 9.62 cm.

From the available data (Table 1) on scanning in 47 cases, uterus was found to be absent in 33 (70.2%). In 34 cases, the gonads were absent in 18 (52.9%) and in the rest it varied [streak gonads (3; 8.8%), right streak gonad / left gonad absent (2; 5.9%), swelling just above mons pubis (2; 5.9%), testicular tissue (15; 14.7%), bilateral ovotestis (3; 8.8%) and right testicular tissue / left ovotestis (1; 2.9%)].

The complete female external genitalia were observed in 36/48 (75%). Ambiguous genitalia with clitoromegaly could be seen in 12/57 (21.1%).

Normal vagina was observed in 13 out of 48 cases (27.1%), blind in 27 (56.3%) and absent in 8 (16.7%).

The secondary sexual characteristics were known in 54 cases (Table 1). The percentage of individuals with normal breast (23, 42.6%) was slightly less when compared to the individuals with hypoplastic (16, 29.6%) and absent (15, 27.8%) breasts.

Normal (6, 11.1%) axillary / pubic hair was observed to be less than the poorly developed axillary / pubic hair (scanty-20, 37%; absent-12, 22%; absent axillary / scanty pubic - 9, 16.7%; scanty axillary / absent pubic - 4, 7.4%; absent axillary / normal pubic - 3, 5.6%).

From Table 2, it can be seen that 12 were born to consanguineous parents. One proband had consanguineous grand parents and one more proband had consanguineous parents and grand parents both on the maternal and paternal sides. Mostly first cousin relationship (66.7%) was observed in the parental consanguinity.

From Table 3, it could be observed that the highly significant features associated with consanguinity were normal axillary hair, ovotestis, absent vagina and significant features were hypoplastic / normal pubic hair, absent gonads and clitoromegaly.
**DISCUSSION**

In the literature, even though the occurrence of XY females in individuals with PA has been reported, information specifically pertaining to the present study is not available. Accordingly the observations of the present study are discussed.

From Table 4 [4-8] it can be seen that in most of the studies, the XY female condition has ranged from 16.7 to 36.7%. In the present study, the observed percentage of 46 XY status in the females referred with PA was 38.3, which seemed to be higher than the range reported in literature. It may be because of the nature of referral for karyotyping and counseling, whether it was for PA, secondary amenorrhea or sterility.

The mechanisms behind the formation of the XY sex reversal are:

A. In the individuals with defective SRY, the XY female condition may be:

1. Mutation / deletion in SRY at the time of paternal gametogenesis. Expression of the SRY gene appears to be one of the first signals in the process of testicular morphogenesis[9, 11].

2. Translocation of SRY region from Y to X during paternal gametogenesis.

B. In individuals with normal SRY, the XY female condition may be due to:

1. Duplications of a region termed “Dosage sensitive sex reversal / Adrenal hypoplasia critical region X” (DAX-1).

2. Mutations in autosomal sex determining regions (9p24.3 (DMRT), 10q26 (SFI), 11p (WT1), 17q23 (SOX9), 10q24a25 (CYP17), 2p23 (SRD5A2), 2q33, 1p35 (Wnt-4)).

3. Mutations in Androgen receptor gene located on X at the region q11\(\alpha\).2.

4. Absence of hormones or defects in the pathways of synthesis of hormones like AMH, testosterone, 5-alpha dihydrotestosterone.

5. The pregnant woman with a male fetus takes high doses of drugs like cyproterone acetate, flutamide and finisteride for the treatment of hirsutism in the first trimester. This could lead to female external genitalia. The cyproterone acetate and flutamide involves blocking the androgen receptor and the finisteride involves inhibition of 5-alpha reductase[11,12].

The XY female individuals lacking androgen receptors are on an average taller than normal females, but average for males. Estrogens are necessary to stop the growth. Persons who lack estrogen continue to grow well into adulthood. The reported average height of the XY females in western studies for testicular feminization syndrome is 172.2 ± 6.5 cm and pure gonadal dysgenesis is 172 ± 7[13].

In the present study, the average height of the XY female individuals was 156.04 ± 9.62 cm. The difference may be due to nutrition or genes or ethnic variation or racial differences.

In general the phenotypic features of the 46 XY females are described as phenotypically female with breast development, sparse axillary / pubic hair, external genitalia varying from normal female external genitalia to ambiguous genitalia and gonads which may be ovaries / testis / ovotestis / streak gonads and 46 XY karyotype.

XY females with complete androgen insensitivity syndrome may show bilateral testes, female external genitalia, a blind ending vagina and no mullerian derivatives. However, fibromuscular remnants and rudimentary fallopian tubes / uterus may exist. Breasts may have normal ductal and glandular tissue, but areolae are often pale and underdeveloped. Individuals with partial androgen insensitivity syndrome have female phenotype, clitoral enlargement and labioscrotal fusion. In the individuals with mutated SF1 gene, the features may be primary adrenal failure, female external genitalia, streak gonads and normal mullerian derivatives responsive to hormones[11].

In the present study, the categorized phenotypic features pertain to either the primary or secondary sexual traits.

In 13 probands with hypoplastic uterus and gonadal dysgenesis / agenesis, mullerian inhibiting substance and testosterone may have been deficient leading to the development of uterus; in one proband with hypoplastic uterus and normal gonad, the Leydig cells may have been defective; in one more case with normal uterus, the testicular portion of the ovotestis might be non-functional.

In 33 probands with absent uterus, the gonads seen were testis, ovotestis, testis / ovotestis and streak gonads. In cases with absent gonads, the gonads, which were normally functioning in the beginning, might have secreted the mullerian inhibiting substance and testosterone, so that the
mullerian duct regressed. Later on, may be the testis disappeared (vanishing testes syndrome) or became streak and could not function properly, the cause of which is not yet known.

In the probands with testis and / or ovotestis, absent uterus may be due to the normal functioning of the gonads leading to the regression of the mullerian duct.

Several genes have been identified in the control of testis determination: SRY, WT1, SOX9, SF1, DAX1, EMX2, LIM1, submicroscopic deletion upstream NR0B1[14-17].

In the present study, absent gonads (18) may be due to the absence or defect or mutation in the genes involved in the determination of testes including SRY or vanishing testes syndrome. Streak gonads / gonadal dysgenesis (5) may be due to the sex chromosomal mosaicism in the gonads even when the karyotypes are normal in lymphocytes.[18]

The incidence of true hermaphroditism (TH) is less than 10% of all intersex cases. Individuals with true hermaphroditism have both ovarian and testicular tissue. The most commonly found gonad is ovotestis, followed by ovaries and testes[19,12]. In the present study, TH individuals had bilateral ovotestis (3) or right testicular tissue / left ovotestis (1). The SRY protein may have initiated the gonadal development, but there could be defect in the other genes downstream of SRY. Post zygotic gonadal mutation in SRY may have resulted in ovotestis or they may be cryptic mosaics for any gene mutation in the gonadal differentiation pathway or have XX cell line.

Dihydrotestosterone is a key hormone for virilization of male external genitalia. 5α-reductase is necessary for conversion of testosterone to dihydrotestosterone. Any mutation in 5α-steroid reductase deficiency type 2 gene (5αSRD2) results in male pseudohermaphroditism[20].

In the present study, 36 had complete female external genitalia and 12 had ambiguous genitalia with clitoromegaly. These abnormalities could be due to the defects in the testosterone pathway or 5 alpha reductase deficiency.

In patients with blind vagina (26) the urogenital sinus might be normal, but the mullerian duct may not have developed. In patients with absent vagina (8) urogenital sinus might have failed to contribute to the caudal portion of vagina.

In the present study, in probands with normal / hypoplastic breast development having ovary and / or ovotestis, ovary or ovarian portion of the ovotestis may have functioned normally, but the testis or testicular component of ovotestis may be abnormal. In normally functioning testis and / or testicular portion of ovotestis, the cyclic pattern of FSH, LH secretion may be similar to that in normal women, a low ratio of testosterone to estradiol caused by enhanced secretion of estradiol by testes and / or ovotestis may have played an important role.

In the probands with absent breasts (27.8%), gonads may be absent or estrogen production might have decreased due to the streak gonads or defective FSH / LH receptors in normal gonads or testis must be functioning normally.

The scanty axillary / pubic hair might be due to decreased production of sex hormones in the probands with streak gonads. In patients with absent gonads hormones produced by adrenal gland may have influenced the development of hair and in probands with testis and / or ovotestis the production of testosterone could be very less compared to estrogen leading to scanty or normal hair. The absent axillary / pubic hair could be because of the absent gonads or the defective testis and / or the ovotestis not able to secrete the estrogen.

Consanguineous marriages are widespread in the world ranging from 2 - 60%, especially in India and that too from South India. The effect of consanguinity could be because of the expression of genes in homozygous condition. Thus, when a single mutated gene is expressed, its effects could be manifold resulting in various malformations of a number of organs and systems leading to a spectrum of phenotypic expression.

In the present study, consanguinity seen in 14 cases may have brought the homozygosity in the genes for the enzyme deficiency resulting in the hormonal imbalance, such as 5- alpha reductase.

Counseling in 46 XY females is very sensitive[21]. The sexual identity has to be closely linked with overall management.

Until late adolescence, testes may be left in place so as to provide the natural source of estrogen and testes could be removed because the risk of developing neoplasia exists.

Estrogen treatment is essential after gonadectomy. Vaginal reconstruction is advised for those who had very short vagina / absent vagina.

Reduction clitoroplasty is to be advised in individuals with clitoromegaly, which allows preservation of neurovascular bundle with normal sensation and cosmetic appearance.

With the consent of parents, appropriate psychosocial support system should be established under which the diagnosis, pathophysiology, quality of life issues may be disclosed to the patient. The affected individuals are repeatedly advised and assured of their potential to lead life as a woman, including marriage except for fertility. Of course, adoptive parenthood is also a feasible suggestion.
The most frequent causes of the 46, XY female, such as autosomal (5 – alpha reductase) or X linked recessive mode of inheritance (androgen insensitivity syndrome) or molecular defects in the Y-linked SRY gene, may be explained along with the risk of recurrence or occurrence.

It is the phenotypic and psychological sexual identity that is more relevant than chromosomal sex. The sex, the gender assigned in infancy is the one the affected individual stays with into adulthood. Great care must be taken not to confuse the affected individuals. Appropriate gonadal hormone replacement therapy should be recommended at the age of puberty.

CONCLUSION

The rationale behind the choice of sample size is to provide for the first time from India a study on such a large sample of 46 XY condition as a source of information. The genotype i.e., 46 XY karyotype and the phenotype i.e., especially the primary and secondary sexual characters have been correlated. The detected genes on the autosomes and the sex chromosomes, the familial disposition and the consanguinity suggest a high degree of genetic component in the etiology. A multi - team approach is provided to the affected individuals and the family.

In the present study, at the time of management and counseling, all the issues are dealt as per the local context which includes the socio- economic – educational – cultural - religious and regional back ground of the 46 XY individuals and their family.

REFERENCES

ABSTRACT

Severe lactic acidosis is a rare but life threatening complication of metformin, particularly in patients with renal failure. The mortality rate of metformin induced lactic acidosis is about 50%. Metformin is usually prescribed in type 2 diabetes and is a recognized cause of lactic acidosis in predisposed diabetic patients. We present a case of anorexia nervosa (AN) admitted with severe lactic acidosis and acute renal failure induced by six months of self medication with metformin attempting further weight reduction. The patient was volume resuscitated and started on bicarbonate infusion. She underwent immediate hemodialysis with rapid and prompt recovery. The relation between metformin induced lactic acidosis and anorexia nervosa is not known before. Reversible tubular dysfunction that may mimic Fanconi syndrome has been documented in one report. AN can be considered an additional risk factor for metformin induced lactic acidosis.

KEY WORDS: anorexia nervosa, lactic acidosis, metformin

INTRODUCTION

Lactic acidosis is a serious clinical condition associated with high mortality. Lactic acidosis is particularly found in conditions associated with impaired tissue oxygenation (type A, e.g., shock states) and those in which a systemic impairment in oxygenation is not apparent (type B). Metformin, commonly used in patients with type 2 diabetes, is rarely associated with lactic acidosis (type B) with an average incidence of 0.03 per 1000 patient-years and mostly in patients with associated renal, hepatic, cardiac or respiratory failure, dehydration and elderly diabetics[1]. If the underlying cause of lactic acidosis can be reversed, lactate will be metabolized and acidosis will resolve. This explains the high mortality rate in such patients. Very rarely however, lactic acidosis can occur as a result of metformin therapy in the absence of pre-existing risk factors as reported in this case.

CASE REPORT

A 20-year-old female patient was admitted to Farwania Hospital with one day history of generalized fatigue, nausea, vomiting, abdominal pain and severe shortness of breath. She was admitted three months earlier with severe weight loss and amenorrhea, and diagnosed as a case of anorexia nervosa (AN). However, she rejected follow up with the psychiatrist. At that time she gave history of taking metformin for weight reduction and she had normal renal and liver function in addition to normal blood glucose measurements. Her father, mother and sister were diabetics on metformin.

On admission, she was confused, hyperventilating and emaciated. Her blood pressure was 90/60 mmHg, pulse 127/min, temperature 35 °C with poor peripheral circulation (cold, cyanosed extremities and mild pedal edema). Her weight was 27 kg and height 162 cm with a body mass index (BMI) of 10.3 kg/m² (normal BMI: 18.5-24.9).

Her initial laboratory findings were as follows: ABG: pH = 6.8 (normal:7.35-7.44), PO2 = 172 mmHg (normal:70-100), PCO2 = 9 mmHg (normal:35-45), HCO3 = 4 mmol/l (normal:21-28). The results of her laboratory investigations are shown in Table 1.

The patient was started on intravenous fluid, sodium bicarbonate and noradrenaline infusion, in addition to massive replacement of calcium, magnesium, phosphorus, folate, vitamins B1, B6, B12 and other trace elements.

The diagnosis of metformin induced lactic acidosis was made and hemodialysis was initiated immediately. She was evaluated by the surgical service and they excluded a surgical abdomen
clinically and by abdominal ultrasound. Next day, patient was fully conscious with improving hemodynamics and rising serum pH and bicarbonate. She developed a picture of DIC (prolonged PT, PTT, PLT count dropped to 44x10^9, low fibrinogen, high FDP) and transient diffuse ECG changes. On the second day, her urine output improved, serum creatinine dropped to 177 mg/l and the DIC parameters normalized. She was further managed in the medical ward and gradual oral feeding was started with supplementary calcium, vitamin D, folic acid and multivitamins without any complications. The patient was under medical, psychiatrist and dietitian’s care in the medical ward for two months and discharged with improving nutritional parameters.

**DISCUSSION**

Metformin (dimethylbiguanide) is an orally administered drug used to lower blood glucose concentrations in patients with type 2 diabetes. Metformin therapy causes a small increase in basal and postprandial blood lactate concentrations, within the normal range. The interpretation of these increases, however, needs to take into account the fact that obesity and diabetes slightly raise blood lactate concentrations. The increased blood lactate concentrations are probably caused by metformin-induced conversion of glucose to lactate by the intestinal mucosa. The lactate then enters the portal circulation and is largely cleared by the liver, in which it serves as a gluconeogenic substrate[1]. When the liver is inundated with fuels after a meal, more lactate gains entry into the systemic circulation[2,3]. Lactic acidosis is a rare but serious adverse effect in metformin-treated patients, with an estimated incidence of less than 0.01 to 0.08 cases (average, 0.03) per 1000 patient-years. In most patients it occurs because one or more contraindications were overlooked, predominantly renal insufficiency, leading to high plasma metformin concentrations. Additional factors that increase blood lactate concentrations are often present — for example, a major illness causing hypotension with low tissue perfusion, other causes of hypoxia, liver disease, or alcohol abuse. In these situations the plasma metformin concentration is not necessarily abnormally high. It is important to realize that blood lactate concentrations become elevated in any patient in whom cardiogenic shock or other illnesses decrease tissue perfusion, and in some reported cases, the metformin was probably an incidental factor and not responsible for the lactic acidosis. Nevertheless, under conditions impairing the oxidative removal of lactate, the reduced rate of removal of lactate from plasma resulting from decreased conversion of lactate to glucose by metformin could cause excessive increases in plasma lactate and, possibly, lactic acidosis[1]. The etiology of lactic acidosis in the reported case is probably multifactorial including hypotension, volume depletion, hypothermia, (all due to anorexia nervosa with the subsequent impairment in renal and hepatic function) and probably metformin overdose. The mortality in reported cases is about 50 percent. The risk of death from lactic acidosis in metformin-treated patients is similar to that of hypoglycemia in sulphonylurea-treated patients. Should a patient have lactic acidosis attributable to metformin, the drug can be removed by hemodialysis[1].

There have been reports of decreased platelet sensitivity to aggregating agents during metformin therapy, possibly due to reduced blood glucose concentrations. Increased fibrinolytic activity and small reductions in plasma concentrations of the fibrinolytic inhibitor plasminogen-activator inhibitor type 1 have also been described[4,5]. The DIC picture developed in the reported case could be explained by the severe lactic acidosis and hypothermia.

### Table 1: Laboratory investigation results

<table>
<thead>
<tr>
<th>Laboratory Investigation</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (Random)</td>
<td>1.3</td>
<td>6.7 - 11.1 (mmol/l)</td>
</tr>
<tr>
<td>Sodium</td>
<td>126</td>
<td>140 - 148 (mmol/l)</td>
</tr>
<tr>
<td>Potassium</td>
<td>6.5</td>
<td>3.6 - 5.2 (mmol/l)</td>
</tr>
<tr>
<td>Chloride</td>
<td>96</td>
<td>100 - 108 (mmol/l)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>3</td>
<td>21 - 32 (mmol/l)</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.75</td>
<td>2.2 - 2.62 (mmol/l)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.67</td>
<td>0.81 - 1.58 (mmol/l)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.69</td>
<td>0.74 - 0.99 (mmol/l)</td>
</tr>
<tr>
<td>Albumin</td>
<td>32</td>
<td>34 - 50 (g/l)</td>
</tr>
<tr>
<td>Amylase</td>
<td>100</td>
<td>25 - 115 (u/l)</td>
</tr>
<tr>
<td>Hb</td>
<td>101</td>
<td>117 - 154 (g/l)</td>
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<tr>
<td>MCV</td>
<td>102</td>
<td>77 - 91 (fl)</td>
</tr>
<tr>
<td>WBC</td>
<td>15.4</td>
<td>4 - 11 * (10^9)</td>
</tr>
<tr>
<td>PLT</td>
<td>317</td>
<td>150 - 440 * (10^9)</td>
</tr>
<tr>
<td>ESR</td>
<td>10</td>
<td>&lt; 20</td>
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<tr>
<td>PT</td>
<td>17</td>
<td>12 - 14 (seconds)</td>
</tr>
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<td>APTT</td>
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<td>&gt; 1000</td>
<td>&lt; 500 (ng/ml)</td>
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<tr>
<td>Urea</td>
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<tr>
<td>Alkaline Phosphatase</td>
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<td>50 - 136 (u/l)</td>
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<td>ALT</td>
<td>972</td>
<td>30 - 65 (u/l)</td>
</tr>
<tr>
<td>Random Cortisol</td>
<td>1750</td>
<td>160 - 1000 (nmol/l)</td>
</tr>
<tr>
<td>B12</td>
<td>1200</td>
<td>174 - 878 (pg/ml)</td>
</tr>
<tr>
<td>Serum Folate</td>
<td>13.5</td>
<td>3 - 17 (ng/ml)</td>
</tr>
<tr>
<td>RBC Folate</td>
<td>614</td>
<td>93 - 641 (ng/ml)</td>
</tr>
<tr>
<td>25 OHVITD</td>
<td>12</td>
<td>23 - 113 (nmol/l)</td>
</tr>
<tr>
<td>iPTH</td>
<td>8.9</td>
<td>1.1 - 7.3 (pmol/l)</td>
</tr>
<tr>
<td>TSH</td>
<td>0.9</td>
<td>0.27 - 4.2 (uIU/ml)</td>
</tr>
</tbody>
</table>
AN is an eating disorder that usually begins in adolescence. Among patients who have AN in adolescence, medical complications may persist into the adult years. No particular nutritional regimen has proved to be superior, as long as adequate calories are supplied. Brisk improvement in nutritional status with few complications resulting from re-feeding occurs when inpatients are started with 1200 to 1500 kcal per day and the intake is increased by 500 kcal every four days to about 3500 kcal (for female patients) and to 4000 kcal (for male patients) per day.

Supplemental overnight naso-gastric feeding may slightly decrease the length of the hospital stay among children but is not routinely recommended. Close monitoring is needed during starvation and re-feeding, including monitoring of vital signs and attention to serious complications that require urgent intervention (e.g., prolonged QT interval or hypophosphatemia with associated weakness, confusion, and progressive neuromuscular dysfunction). This syndrome is most common among patients weighing less than 70 percent of their ideal body weight and in those receiving parenteral or enteral nutrition, although it can also occur in those receiving vigorous oral re-feeding. Slower re-feeding minimizes the risk of serious complications. Phosphorus, magnesium, and electrolyte levels and renal function should be followed closely, and supplements should be administered as needed. Short-term medical stabilization alone is inevitably insufficient. To achieve full remission, ongoing care after discharge from the hospital is essential.

AN has been associated with abnormal osmoregulation and impaired urinary concentrating capacity. Conflicting results suggest that the disorder may be related to hypothalamic dysfunction and/or a primary renal defect. The role of antidepressants, which are increasingly prescribed in AN patients, has not been evaluated. AN has been associated with various renal function abnormalities, including a decline in glomerular filtration rate (GFR), an impaired water diuresis, a decreased urinary concentrating capacity and various electrolyte abnormalities. Reversible tubular dysfunction that mimics Fanconi syndrome has also been described in one report.

In conclusion, lactic acidosis is a serious complication of metformin use in diabetic patients if not used selectively. The relationship between metformin and anorexia nervosa in patients not known to be diabetic has not been described before, but, it makes sense to avoid it in such patients given the fact that AN can cause complications virtually affecting every organ system.

REFERENCES

Case Report

Giant Coronary Artery Aneurysms in a Young Infant with Kawasaki Disease

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ABSTRACT
We report the case of a young infant with prolonged fever and delayed diagnosis of Kawasaki disease which was complicated with development of multiple large coronary aneurysms.

KEY WORDS: coronary artery aneurysm, fever, Kawasaki disease

INTRODUCTION
Infants with Kawasaki disease (KD) are at increased risk of having coronary artery abnormalities[1]. Moreover, coronary artery aneurysms occur significantly more often in those infants with delayed diagnosis[2-3]. Therefore, health care providers should have a high index of suspicion for KD in young children presenting with prolonged fever and rash without an obvious focus of infection. We report a case of KD in a very young infant with delayed diagnosis and treatment who subsequently developed multiple coronary artery aneurysms.

CASE REPORT
A two and half month old Kuwaiti male infant was admitted to our hospital with peeling of the fingers. Three weeks prior to this admission he was admitted to another institution with history of fever (39.5 °C) of two days duration and irritability. Septic work up was done and he was treated as a case of urinary tract infection with antibiotic because of pyuria. On the third day from the onset of fever he developed generalized erythematous maculopapular rash. A drug reaction was suspected and the antibiotic was changed. By the fifth day of his febrile illness he developed bilateral non-exudative conjunctivitis and lymphadenopathy. Cultures were negative and the patient was discharged home after one week of hospitalization. He continued to have intermittent low grade fever for another seven days and started to have peeling of the fingers and toes.

On admission, he was afebrile with normal pulse and blood pressure. Clinical evaluation showed peeling of the fingers and toes, and the rest of the physical examination was unremarkable.

His blood investigations showed: White Cell Count: 6.1 X 10⁹/l, Platelets count: 760 X 10⁹/l, Hemoglobin: 9 (g/l), Erythrocyte Sedimentation Rate: 80 mm/hour, Serum Albumin: 28 (g/l), and normal renal and liver function tests. Chest radiograph, abdominal ultrasound and electrocardiogram were normal.

Echocardiography showed multiple saccular aneurysms involving all coronary arteries - left main, left anterior descending, left circumflex and right coronary artery. Some of these aneurysms were measuring up to 8 mm in diameter and thus labeled as giant aneurysms (Fig. 1 and 2).

DISCUSSION
KD is one of the most common vasculitides in childhood. Owing to a lack of diagnostic tests, the diagnosis is based on clinical criteria after the exclusion of other febrile illnesses in young children[1]. KD mainly occurs in infants and young children[2]. In one Japanese series only 1.7% of patients were < 3 months old[3]. The youngest reported patient is a two week old infant who had classical features of the illness[4]. In infants, the atypical presentations (longer duration of illness before diagnosis, lower incidence of conjunctivitis, lower incidence of skin rash, lower incidence of extremity changes, and lower C-reactive protein) are common and this may result in delayed diagnosis and treatment[4-5]. A rapid and severe coronary artery involvement is also more common in infants[6-7]. Some cases have been reported with giant coronary aneurysms,
which by definition is an aneurysm whose diameter exceeds 7 mm\[^6\].

This case emphasizes the fact that KD must be suspected in any child with persistent high fever even in the absence of all diagnostic criteria on initial presentation. Intravenous immunoglobulin can be recommended before all the typical manifestations are present\[^8\]. Delayed treatment might be responsible for coronary artery complications like ectasia or aneurysm, myocardial infarction, peripheral extremity gangrene and even sudden death, especially in infants\[^6,9-11\].

Pediatricians should be aware that KD occurs in neonates and young infants, the presentation may be atypical, and it can follow a rapid and severe course\[^4\].

To prevent the development of cardiac sequelae, in particular giant coronary aneurysms, gamma-globulin therapy should be started as soon as possible\[^12\].

**CONCLUSION**

Clinical diagnosis of KD in the newborn and during the infancy period requires a high index of suspicion. Early diagnosis and treatment are important to prevent coronary artery aneurysms which occur significantly more often in patients with delayed diagnosis. More instructions and continuing medical education are needed to teach health care providers to have a high index of suspicion for KD in young children presenting with illnesses associated with fever and / or rash. Echocardiography helps to confirm the diagnosis and should be performed in all suspected cases.

**REFERENCES**

Case Report

Vertebrobasilar Artery Dissection Complicating Cervico-Dorsal Intramedullary Ependymoma: A Case Report

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ABSTRACT

Vertebral artery dissection (VAD) is an important cause of posterior circulation stroke in young adults. It could be either spontaneous or traumatic; initial symptoms are often non-specific, and diagnostic arteriography is not performed until neurological deficits are obvious. We describe a rare case of a patient who presented with cervico-dorsal intramedullary ependymoma, and developed brain stem infarction caused by vertebrobasilar artery dissection during her postoperative period, which was diagnosed by Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA). Although vertebrobasilar artery dissection is rare, it should be considered in the differential diagnosis of brain stem infarction, and urgent MRI / MRA should be done as it is a reliable diagnostic tool and less invasive compared to cerebral angiogram.

KEY WORDS: brainstem infarction, ependymoma, MRI, vertebrobasilar artery dissection

INTRODUCTION

Vertebral artery dissection (VAD) is an important cause of posterior circulation stroke in young adults. Spontaneous dissection is associated with a large number of conditions such as fibromuscular dysplasia (FMD), Marfan’s syndrome, homocystinuria, moy-a-moya disease, syphilitic arteritis and strenuous physical activity[1]. The main pathophysiological changes are hemorrhage outside the vascular lumen due to trans-intimal extravasation of blood, dissection of the internal elastic membrane from the intima causing narrowing of the true lumen, and subsequent thrombosis with or without occlusion of the lumen[2,3]. It is most common among middle-aged patients and the vertebrobasilar system was the commonest site reported in large series. Clinically, VAD presents with headache, neck pain, and TIA / stroke picture[4]. Commonly, occlusion of the third or fourth portion of the vertebral artery happens, leading to lateral medullary syndrome or cerebellar infarction. Unfortunately, as the initial symptoms are non-specific[5], diagnostic arteriography is not performed until neurological deficits are obvious[6].

CASE REPORT

A 42-year-old lady presented with a long history of neck pain, progressive paraparesis, and sphincteric disturbances. She had a past history of cardiac arrhythmias. MRI scan (Fig. 1) revealed cervico-dorsal intradural intramedullary tumor extending from C7 to T3 with a spinal cord syrinx above and below the lesion. Lamincetomy of C6, 7, T1, T2 levels with excision of the intramedullary lesion was done. Histopathological examination revealed that the lesion was an ependymoma (Fig. 2). Few days later, she developed sudden headache, drowsiness and right upper limb weakness. Emergency CT brain was normal. Emergency MRI / MRA of the brain revealed pontine / upper medullary infarction, with dissection of the right vertebral and lower basilar arteries (Figs. 3 and 4). Patient was immediately commenced on heparin for one week followed by aspirin 81 mg, and clopidogrel bisulfate 75 mg (Plavix). Her neurological status improved only slightly, and few months later she died because of septicemia.

DISCUSSION

Spontaneous VAD has been reported to be associated with FMD, Marfan’s syndrome, homocystinuria, sudden head motion or unrecognized or forgotten trauma[1]. In our case, we believe that surgical trauma caused by the patient being maintained on the operating table for a long time during surgery in a certain position (prone, with the head turned to right side) was the most likely precipitating factor for VAD.
The clinical signs of VAD vary from silent stroke to major posterior fossa stroke. Berkovic et al reported 31 patients with intracranial vertebrobasilar artery dissection where 28 showed one or more clinical symptoms. In three patients, the vertebrobasilar artery dissection was discovered incidentally. The initial symptoms in 28 patients were brain stem and / or cerebellar related symptoms. However, some patients had only mild symptoms such as headache, vertigo or tinnitus. Sixteen patients had co-morbid conditions (some of them had two diseases): seven patients had hypertension, six had diabetes mellitus, four had cerebral infarction, two had angina pectoris, one had hyperlipidemia, one had cerebral aneurysm and one had abdominal aortic aneurysm.
The pathophysiologial changes described in dissection of an artery include hemorrhage outside the vascular lumen due to trans-intimal extravasation of blood, and dissection of the internal elastic membrane from the intima causing narrowing of the true lumen. However, embolism from the dissected segments of the vessel is not usually involved in the pathologic process, despite various reports indicating that thrombus extension or dissection leading to occlusion of arterial branches, are responsible for the pathology. Sometimes, an obvious isolated process is not apparent, and a combined process of thrombus propagation, dissection progression and embolization would contribute to the pathology together[8]. Either pathologic process would cause some degree of basilar artery occlusion, and might involve a large number of brainstem structures. Many brainstem syndromes resulting from particular infarction patterns have been described: medial and lateral medullary; inferior / middle / superior pontine; midbrain tectum and tegmentum; posterior cerebral territory. These were labeled with eponyms such as Wallenberg, Benedikt, Weber, Parinaud, and top of the basilar[9]. Any of these hypoperfusion syndromes may instead be symptoms of vertebrobasilar migraine. Of course, complete obstruction of the basilar flow will result in coma and probably death, if collateral flow from the anterior circulation does not come through the circle of Willis. In our patient, the physical finding of bilateral weakness, right greater than left, was probably due to thalamic infarction at the border of the posterior limb of the internal capsule. This pattern is consistent with the clinical picture of persistent mild hemiparesis.

Since MRI is superior in the diagnosis of vertebrobasilar ischemia, the role of MRI and MRA in the detection of dissections of the vertebral artery was retrospectively analyzed. Between 1989 and 1995, Erro et al reported and analysed 24 patients with a VAD and one patient with a basilar artery dissection (8 female and 17 male; age ranged 23-60 years, mean 41.2 years). The diagnosis of VAD (14 left VAD; 9 right VAD; 1 bilateral VAD; 1 basilar artery) was established by Digital Subtraction Angiography (DSA). Subsequently, all patients underwent a combined MRI / MRA examination protocol at 1.5 T that consisted of multiplanner different sequence and time of flight MRA of the intra and extra cranial arteries 3D sequences. The MRI / MRA findings were correlated to DSA and ultrasound results. During the acute and sub acute stage, MRI / MRA revealed abnormal findings in 21 of 25 dissected vessels (95.5%). There was one false-negative MRI / MRA in a patient with a VAD (intimal flap without peripheral flow disturbances). In 7 / 25 VAD the MRI / MRA findings were rated specific[10].

Another study analyzed the MRI findings of 31 patients (20 men and 11 women) with intracranial vertebrobasilar artery dissection, confirmed by vertebral angiography[9]. The MRI findings suggestive of arterial dissection include: arterial intramural hematoma on T1-weighted images, intimal flap on T2-weighted images, and double lumen and enhancement of wall and septum on contrast-enhanced 3D-spoiled gradient – recalled acquisition (SPGR) images. The positive rate of intramural hematoma was not satisfactory (32%); the finding of double-lumen on contrast-enhanced 3D-SPGR was present in 87% of the patients, and this was considered useful for the screening of vertebrobasilar artery dissection. The study suggested that arteriography may be necessary for the definite diagnosis of intracranial vertebrobasilar artery dissection[9].

The typical finding on angiography is the pearl string sign; but it is not necessarily observed in all cases. It may sometimes be difficult to delineate arterial wall dissection by conventional angiography particularly in cases where post-mortem histopathologic examination revealed pseudo-lumen, intimal flap and intramural hematoma. Recent advances in MRI have enabled us to delineate the dissection of an artery more clearly, and this has become a valuable clue in the diagnosis of such rare cases[6,11].

CONCLUSION
Urgent MRI/MRA brain should be performed in patients presenting with bulbar palsy and tetraparesis following cervicodorsal surgery to determine the possible co-existence of vertebrobasilar artery dissection, as occurred in this rare case. Cerebral angiogram may not show the existence of a dissection.

ACKNOWLEDGMENT
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Case Report

Pyridoxine for Severe Metabolic Acidosis and Seizures due to Isoniazid (INH) Overdose

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ABSTRACT

Isoniazid (INH) overdose can be effectively treated, only if, suspected. Seizures and coma are due to INH unless proved otherwise in patients with access to the drug. Acute INH intoxication is characterized by a clinical triad consisting of metabolic acidosis resistant to treatment with sodium bicarbonate, seizure which may be fatal and refractory to standard anticonvulsant therapy, and coma. Pyridoxine is the specific antidote for INH overdose. We report a case of a 25-yr-old lady, who in a suicidal attempt ingested a toxic dose of INH resulting in status epilepticus and was successfully treated with pyridoxine (Vit B6)

KEY WORDS: INH, pyridoxine, seizures

INTRODUCTION

Since its introduction in 1952, Isoniazid (INH) has remained one of the drug of choice in the prophylaxis and treatment of tuberculosis (TB)[1]. It is the most widely used of the anti-tuberculosis drugs and most physicians are aware of the use of liver function tests to detect hepatotoxicity in patients who are being treated with INH. However, physicians may not be aware that the acute ingestion of as little as 1.5 gm of this drug can be toxic. Consuming 80 mg per kg (sixteen tablets of 300 mg each in a 60 kg person) or more intentionally or accidentally has a high likelihood of leading to recurrent seizures, profound metabolic acidosis, coma and even death, if not recognized. Pyridoxine should be infused immediately by slow intravenous push, even if the patient is fully conscious. The earlier pyridoxine is given, the fewer the complications[2].

CASE REPORT

This 25-year-old lady was started on INH 300 mg / day about four months earlier after being diagnosed to have tuberculous cervical lymphadenopathy. She began convulsing at home half an hour before arriving to the hospital.

She was brought unconscious to the ER by her family members who informed the emergency physician that the patient was on anti TB treatment and an empty bottle of 50 tablets of INH (150 mg) was found at home. So it appeared that an unknown amount of INH was ingested by the patient in an attempt to commit suicide after a disagreement with her husband. One hour after ingestion, she collapsed and started seizing repeatedly. Her medical history was otherwise unremarkable.

Three seizures were witnessed in the emergency room. Diazepam was administered intravenously in addition to IV phenytoin without any control over the seizures.

A physical examination revealed a 70 kg female who was verbally unresponsive but regained her consciousness between the attacks of seizures. The other physical findings were normal. Neurological examination revealed no focal abnormalities and deep tendon reflexes were normal. There was no clonus and the plantar response was normal. Blood gas measurement revealed an arterial pH of 7.2, partial pressure of arterial oxygen (PaO2) 10 kpa, PaCO2 4.5 kpa and bicarbonate concentration of 15 mmol/l. In view of the history of consuming an unknown amount of INH, we gave her a total of 10 gm of pyridoxine tablets (crushed and given as slurry through the nasogastric tube). Gastric lavage was done in ER earlier. We tried to get IV pyridoxine but it was not available at that time in our hospital. Administration of pyridoxine led to cessation of the seizures and to the improvement of acid base status. The pH became 7.41, PaO2 22.6 kpa on oxygen mask, PaCO2 4.2 kpa, HCO3 20 mmol/l.

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four hours later. The patient was admitted to ICU for observation and was not intubated. There was no subsequent seizure activity. Her CBC, urea and electrolyte, random blood sugar, S. calcium, liver enzymes, renal function and coagulation profile were all within normal values. CT brain was done and was normal. Lactic acid level was normal. She was stable and shifted to the general ward the next day.

She was evaluated by a psychiatrist who reported no evidence of major psychiatric illness. Two days after admission, her liver enzymes started to rise gradually and reached a peak of AST 100 U/l, and ALT 88U/l on day 6. These values gradually dropped to normal while bilirubin, alkaline phosphatase and prothrombin time remained normal all the time.

The patient was discharged well after 10 days and was advised to take only the recommended dose of INH.

DISCUSSION

INH toxicity is associated with high mortality rate. If INH is taken acutely, as little as 1.5 gm can cause toxicity. Doses larger than 30 mg per kg often produces seizures. Ingestion of the drug in amounts greater than 80-150 mg / kg can rapidly lead to death[1]. The signs and symptoms of INH toxicity may appear within 30 minutes to two hours after ingestion and may include nausea, vomiting, rash, fever, ataxia, slurring of speech, dizziness and stupor. These symptoms are usually followed by grand mal seizures and coma.

The seizures are often refractory to anticonvulsants and respiratory failure and death can follow. Acute INH overdose is associated with a clinical triad consisting of: seizures refractory to conventional therapy, severe metabolic acidosis and coma. INH level can be measured but blood levels are not helpful in managing an acute INH overdose.

Our patient presented with severe acute INH toxicity and to the best of our knowledge, this is the first and only case of INH induced seizures reported from our hospital and possibly in Kuwait. She was successfully treated with large doses of pyridoxine (Vitamin B6) with complete recovery. INH is thought to cause seizures by interfering with the aminobutyric acid synthesis[2]. Specifically, INH inhibits glutamic acid decarboxylase, by inhibiting pyridoxal 5 phosphate aco-factor for glutamic acid decarboxylase enzyme. The consequent reduction in GABA level increases the susceptibility to seizures[3]. These neurological effects of INH are specifically countered by administration of pyridoxine. Pyridoxine, in a dose equivalent to the amount of INH ingested is the only effective antidote. When conservative therapy fails or in case of renal insufficiency, dialysis must be considered. The earlier pyridoxine is given, the fewer the complications. In case of INH toxicity pyridoxine should be administered in a dose equivalent to the suspected amount of INH ingested (i.e. gram per gram replacement)[5]. If the amount of INH ingested is unknown or if INH overdose suspected, first flush INH with 5 gm of pyridoxine, repeat the initial dose at 5-20 minute intervals until the patient becomes stable or the dose of ingested INH is exceeded 1 ½ times by the dose of pyridoxine.

Pyridoxine is effective in treating not only INH induced seizures but also the mental status changes associated with this overdose. The dose required to induce awakening may be higher than that required to control seizures.

CONCLUSIONS

- INH toxicity should be suspected in any patient who presents with refractory seizures and metabolic acidosis.
- As tuberculosis increases and physicians prescribe more INH, a consequent increase in accidental and intentional ingestion of this drug should be expected. Physicians must be prepared to counteract potentially fatal toxic effects of INH.
- Recommended pyridoxine dose is 5 gm IV for an unknown ingestion. When the quantity of INH ingested is known, administer a gram of Vitamin B6 for every gram of INH ingested.
- When IV pyridoxine is unavailable or its supply is not sufficient to treat significant INH overdose, oral tablets could be crushed and infused through a naso-gastric tube.
- Prognosis is good when treatment is instituted early.

REFERENCES

Case Report

Difficulties in the Diagnosis of Familial Hemophagocytic Lymphohistiocytosis

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is characterized by proliferation and non-malignant activation of histiocytes and T lymphocytes in the reticuloendothelial system. Diagnostic guidelines include fever, splenomegaly, cytopenia, hypertriglyceridemia and / or hypofibrinogenemia with hemophagocytosis in the bone marrow, spleen or lymph nodes. In many patients diagnosis is difficult due to lack of diagnostic criteria, hemophagocytosis, variability of clinical presentation, spontaneous improvement and the absence of a specific marker of the disease. When there is strong clinical suspicion of familial hemophagocytic lymphohistiocytosis (FHL), chemotherapy and immunosuppressor treatment should be started early to achieve complete cure and should be followed by hematopoietic stem cell transplantation. We present a case of a 13 months old boy who presented with fever, anemia and thrombocytopenia, enlarged liver and spleen, hyperferritinemia, hypertriglyceridemia and hypertransaminasemia without the finding of hemophagocytosis in the bone marrow. The patient improved spontaneously but presented with reactivation of the disease six weeks later and died after few weeks.

KEY WORDS: familial hemophagocytic lymphohistiocytosis (FHL), hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life threatening condition caused by the disturbance of regularity of the immune system on the basis of various inherited or acquired immune deficiencies[1]. It is classified as a 2nd class of histiocytosis. There are no histological and / or cytological findings that are specific for HLH and the diagnosis must be based on additional clinical and laboratory investigations, including NK cell activity and also preferably genetic studies[2]. The diagnosis may be difficult and unfortunately a hallmark (hemophagocytosis) is usually not found on the initial bone marrow examination[3]. The identification and specific precocious treatment provides the possibility of curing many HLH patients.

CASE REPORT

A 13-month-old Syrian boy presented with high grade fever, vomiting and erythematous skin rashes over lower limbs for one week. He was active with good appetite. His parents are consanguineous with no family history of blood diseases or a similar condition. On examination, he looked well-grown, pale, not jaundiced with a hepatomegaly of 4 cm and splenomegaly of 6 cm, no significant lymph nodes enlargement and normal neurological examination. His investigation results were as follows: WBC - 8.2 x 10^9 (poly 15%), Hb 85 g/l, platelets 77 x 10^9, Transaminases; ALT 120 u/l, AST 135 u/l, total bilirubin 17 umol/l and direct bilirubin 6 umol/l. Coagulation profile, total protein and albumin were normal. The triglycerides (3.46 mmol/l), LDH (461u/l) and ferritin (3000 ng/ml) were increased.

Sequencing of coding regions of perforin gene at locus 10q21-22 did not detect any mutations. Immunoglobulin electrophoresis, antinuclear antibodies and extensive microbiological studies were normal. Organic acids analysis in urine using gas chromatography/mass spectrometry (GC/MS) did not detect abnormalities in the pathway of glycolysis, gluconeogenesis, amino acids, ammonia or fat metabolisms. The abdominal radiography confirmed hepato-splenomegaly while rest of the organs were normal. The study of osseus medulla revealed normal bone marrow with no blast cells. During admission he received IV antibiotics and required blood transfusion. His clinical evaluation was favorable and he was discharged after two weeks with a normal blood picture and liver

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function tests.

He remained asymptomatic for about six weeks, and then became sick again with high fever, right-sided focal convulsion which was repeated during the course of his illness. He was treated with phenobarbitone and IV antibiotics. Antifungal drugs (ambisone and itraconazole) were added later when fever persisted. Clinically, he was pale, irritable with right convergent squint, no other neurological deficit, marked hepatosplenomegaly and no significant lymphadenopathy. Fundus examination revealed early papilledema.

Investigations showed the following; WBC 2.2 x 10^9/l (poly 25%), Hb 75 g/l, platelets 34 x 10^9/l, increase in triglycerides (3.8 mmol/l), ferritin (5081 ng/ml), and LDH (956 u/l), transaminases; ALT 37 u/l, AST 50 u/l, coagulation profile; PT 13.8 seconds, INR 1.29, APTT 43.5 seconds, ratio 1.4, and fibrinogen level 102 mg/dl.

MRI of brain revealed multiple ring enhancing lesions in supra-tentorial brain parenchyma mainly at gray/white matter junction with calcification, and generalized brain atrophy. E.E.G revealed abnormal record with sharp waves in left centro-temporal leads. New aspiration of osseus medulla revealed; diffuse non-malignant histiocytes infiltration with prominent hemophagocytosis and increased megakaryocytes with bizarre morphology and tendency to cluster. Erythropoiesis was prominent with megaloblastic features and myeloid activity was reduced, a picture consistent with HLH. The clinical course, prognosis, treatment was explained to the parents and he was started on induction therapy according to HLH – 94 – protocol (Immunotherapy+B.M.T).

Unfortunately he developed severe septic shock, disseminated intravascular coagulopathy (DIC) with pulmonary hemorrhage and died in the pediatric intensive care unit (PICU) despite extensive attempts at resuscitation.

DISCUSSION

HLH is a rare disease. The incidence of primary HLH in children was estimated in Europe to be one per 50,000 live births. The primary form, familial HLH, is typically seen during infancy and early childhood, and is almost invariably fatal with median survival without therapy of two months after onset. A secondary form, sometimes termed “virus associated hemophagocytic syndrome (VAHS) can affect all ages and is associated with high mortality[4]. Primary and secondary forms of HLH may be difficult to distinguish clinically and histologically. Familial affection or parental consanguinity strongly suggests FHL. HLH whether familial or acquired share one common feature, namely a highly stimulated but ineffective immune response that threatens the life of the patient and may lead to death unless arrested by appropriate treatment[5]. Genetic studies showed mutations in the perforin gene in 20-40% of the affected individuals. A second gene that may cause the disease is mutation in Munc 13-4 gene[6].

The clinical picture of HLH is due to an increased inflammatory response caused by hypersecretion of pro-inflammatory cytokines such as interferon-γ (IFNγ), tumor necrosis factor α (TNFα), interleukin IL-6, IL-10 and macrophage-colony-stimulating factor (M-CSF)[7]. These mediators are secreted by activated T-lymphocytes and histiocytes that infiltrate all tissues and lead to tissue necrosis and failure. In spite of the excessive expansion and activation of cytotoxic cells, patients with HLH have severe impairment of cytotoxic function of NK cells and cytotoxic T-lymphocytes (CTLs)[8].

The clinical symptoms of FHL are characteristic but non-specific. The cardinal manifestations of FLH are prolonged fever, hepato-splenomegaly and cytopenias. Lymphadenopathy, icterus or neurological symptoms such as cranial nerve palsies or seizures may also be present. Neurological symptoms may dominate the presentation as in our case thereby causing delay in the diagnosis of the disease. MRI or CT scan of the brain may show abnormalities representing areas of past or ongoing inflammatory activity or demyelinization. Bleeding, atrophy and brain edema may also be found. Hyperdense areas on CT may falsely be interpreted as calcifications[9]. Characteristic laboratory findings include high triglycerides, ferritin, transaminases and bilirubin and decreased fibrinogen.

Hemophagocytosis is found in only minority of cases, but usually develops as the disease progresses. The activity of NK cells and CTLS cells is impaired or absent. The diagnosis of HLH requires that five out of eight criteria be fulfilled, namely; 1) fever, 2) cytopenias (two of 3-lineages), anemia (Hb < 90g/l), platelets < 100 X 10^9/l, neutropenia < 1.0 X 10^9/l), 3) splenomegaly, 4) hypertriglyceridemia (fasting > 3.0 mmol/l) and / or hypofibrinogenemia (< 1.5 g/l), 5) hemophagocytosis in bone marrow, spleen or lymph nodes, 6) low or absent NK- cell activity, 7) hyperferritinemia (> 500 mg/l) and 8) high plasma levels of soluble CD25 (i.e., soluble IL-2 receptor > 2400 u/l)[10].

A number of patients do not manifest five criteria for diagnosis. Thus, when there is strong clinical suspicion of the disease, therapy should be started before overwhelming disease activity causes irreversible damage and response to treatment become less likely. The age of patient, parental consanguinity, and absence of specific infection lead to the diagnosis of FHL in our patient[11]. The
immediate aim in treatment of any patient with HLH is to suppress the severe hyperinflammation that is responsible for life threatening symptoms. Another aim is to kill pathogenic infected-antigen presenting cells and thus remove the stimulus for ongoing but ineffective activation of T lymphocytes. Treatment with chemotherapy and immunosuppression is well known and actually the protocol HLH 94 attains near 50% survival of patients and this should be followed by hematopoietic stem cell transplantation[12]. With regard to long term survival, the prognosis is likely to depend upon the result of bone marrow transplantation which is also becoming increasingly rewarding.

CONCLUSION

It is important to be aware of these diseases as many of the cardinal symptoms are found in immune-competent patients in response to an infectious organisms. But the progression of organomegaly, blood count changes and biochemical parameters should alert the physician to this syndrome since effective and potentially life saving therapy is available.

ACKNOWLEDGMENTS

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Case Report

Neonatal Cardiac Failure - A Pulsating Brain

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ABSTRACT
Arterio-venous malformations should be considered in the case of neonatal cardiac failure with normal echocardiogram. A rare case of Vein of Galen Aneurysmal Malformation (VGAM) resulting in neonatal high output cardiac failure is reported. Clinical presentation, imaging techniques, and prognosis of this disorder is discussed. The advance in management including endovascular embolization at special centers and the outcome is outlined.

KEYWORDS: endovascular embolization, high output cardiac failure, transcranial sonography, VGAM

INTRODUCTION
Congestive heart failure in the neonate is usually due to intracardiac anomalies or cardiac dysfunction. Extracardiac causes are rare. Aneurysmal malformations of the vein of Galen (VGAM) typically result in high-output congestive heart failure or may present with developmental delay, hydrocephalus, and seizures.[1-3]

CASE REPORT
A 12-days-old Kuwaiti girl presented with a history of recurrent apnea attacks, cyanosis and poor feeding since the age of three days. She was the third child of non-consanguineous parents, delivered at term after an uneventful pregnancy. The father has asymptomatic mitral valve regurgitation. The baby’s uncle had a complex cyanotic congenital heart disease, which required surgical correction. Clinically, on admission the baby was found to have tachypnea, tachycardia, gallop rhythm and grade III / VI systolic murmur over the precordium. Her blood pressure was normal in four limbs and she required an FiO₂ of 30% to maintain normal saturation. Her chest X-ray showed a cardiothoracic ratio of more than seventy percent. Her electrocardiogram showed a right axis deviation with right ventricular hypertrophy. The initial arterial blood gases showed a metabolic acidosis with a significantly raised lactic acid. A provisional diagnosis of congenital heart disease was made. The baby was promptly transferred to the pediatric cardiology unit.

A cardiac echogram revealed the following abnormalities:
• Dilated right atrium with a dilated and hypertrophied right ventricle,
• Small atrial septal defect (ASD), ostium secundum type measuring 5 mm, with left to right shunt,
• Severe tricuspid regurgitation (TR),
• Pulmonary artery systolic pressure of 36 mm Hg,
• Normal left ventricular (LV) function.

According to the above clinical and ultrasonic findings, a diagnosis of cardiomyopathy secondary to sepsis was made. Thus, the baby was commenced on anti-bacterial therapy in combination with diuretics. Three days later, the baby was transferred back to the referring hospital.

The baby continued to have tachypnea, tachycardia with gallop rhythm although a repeat chest X-ray showed normal heart size. A repeat echocardiogram, a week later, showed dilated right atrium, a normal right ventricle, no tricuspid regurgitation and normal pulmonary artery pressures with good LV function. Furthermore, her thyroid function tests were within normal limits. Thus, the persistence of tachypnea, tachycardia, gallop and prominent neck pulsations was an indication of high output cardiac failure.

A trans-cranial Doppler ultrasound showed a large hypoechoic area in quadrigeminal plate cistern area. Color Doppler revealed a pulsatile vascularity with arterial feeders. In the coronal view...
the hypoechoic area was in the midline and in the mid-sagittal view in the region of the quadrigeminal plate cistern (Fig. 1 and 2).

A diagnosis of Vein of Galen Aneurysmal Malformation (VGAM) was made. An MRI and an MRA (magnetic resonance angiogram) confirmed the diagnosis. It showed multiple signal void structures in the peri-mesencephalic, ambient and quadrigeminal cisterns. There were multiple arterial feeders directly into the area without an intervening arterial network. Branches from choroidal vessels, pericallosal artery, posterior cerebral artery and a small feeder from middle cerebral artery were noted. The vein of Galen, sigmoid sinus and straight sinus were dilated (Fig. 3 and 4). The myelination pattern of the white matter in the cerebral hemispheres was normal. Brain stem and cerebellum were normal. There was no brain atrophy, encephalomalacia or hydrocephalus.

At five months of age a clinical assessment was carried out. It showed normal growth parameter. A loud bruit over the anterior fontanel was heard for the first time. She had no neurological deficit or cardiac failure. She was referred to a tertiary center in France where interventional therapy was carried out.

**DISCUSSION**

VGAM was first reported in 1937[1] and represents a rare intracranial vascular anomaly typically found in neonates, infants and the pediatric population. It accounts for 30% of the pediatric vascular malformations[2]. A detailed review of the embryologic mechanisms as recognized by Rayband and Strother[3] landmarks a large median prosencephalic vein (normally absent in the adults) into which multiple arterio-venous shunts drain. This vessel known as M Pros V of Markowski[4] or the median prosencephalic vein of Markowski assumes the venous drainage of the brain at the choroidal stage of brain vascular development. The anterior segment regresses and only the posterior segment of M Pros V will persist as the great cerebral vein, or vein of Galen. The arterial supply of VGAM is derived from choroidal arteries. As a consequence of the shunts, the anterior segment of M Pros V, instead of regressing, progressively enlarges under the stress produced by high pressure inflow from choroidal feeders.

VGAM can present in the neonatal period (as in our case), in infancy, in the older child or adult. The three clinical manifestations correlate to the age at
presentation\textsuperscript{[5]} and depend on the angioarchitecture and hemodynamic characteristics of VGAM.

In the neonates almost 94\% of cases presents with cardiac failure and cardio-respiratory alterations. The high cardiac output failure due to volume overload rapidly induces cardio-respiratory distress. In infants hydrocephalus is the presenting feature, occasionally accompanied by seizures. Small VGAM presents in older children and adults with headache.

In our case the initial assessment at the cardiac centre showed features of overloaded right heart. These findings could not account for the persistence of high output cardiac failure. Although initial treatment with diuretics treated the cardiomegaly as well as the overloaded right heart it did not fully resolve the high output cardiac failure. Therefore, an intracranial vascular malformation, as a non-cardiac cause for high output failure, was suspected.

In such cases, where intra-cranial vascular malformations are suspected, Trans-fontanel Doppler sonography can be deployed as a quick and a non-invasive bedside technique\textsuperscript{[6]}. It can also be used to monitor the hemodynamic repercussion of the treatment. In addition, it does not require the anesthetic support needed to perform a CT or an MRI.

The imaging and classification of VGAM as proposed by Yasargil et al has the advantage of clinical usefulness and simplicity\textsuperscript{[7]}. Type I shunt consists of high flow shunts located within the wall of the aneurysm. This type of shunt as in the case under discussion causes a clinical presentation of high output cardiac failure early in the neonatal period due to the very high pressure flow that result from direct arterial flow. Type II or the mural type, in contrast, has an arterial network between the feeders and venous aneurysm itself, usually located in the quadrigeminal plate cistern, and these results in less severe increase of the blood flow. This type of malformation usually presents in infancy with hydrocephalus. Type III is a combination of type I and type II resulting in type I and II changes as well as encephalomalacia. Type IV is in essence a VGAD (Vein of Galen Dilatation) representing a different entity which is actually an independent cerebral arterio-venous malformation that drains into the vein of Galen causing its dilatation.

The imaging techniques including fetal and neonatal USS and MRI, allow early detection and classification of the VGAM. It also helps in determining the prognosis. The presence of brain atrophy carries a poor prognosis\textsuperscript{[8]}. In our case detailed MRI and MRA revealed normal brain structure and hence the benefit of interventional management strategies. The advent of endovascular therapy via trans-arterial or trans-venous route has radically changed the treatment and prognosis of VGAM patients\textsuperscript{[9]}. The cardiovascular repercussions of the AV shunts can be controlled with a minimally invasive approach\textsuperscript{[10]}. Super selective embolization of the feeding choroidal arteries using N-butyl-cyanoacrylate glue has been reported by Friedmann et al in a series of 11 neonates in 1993\textsuperscript{[11,12]} in which no mortality occurred with six (55\%) patients remaining functionally normal at 30 months follow up. Lasagnas et al in 1996 have presented a series of 78 neonates, infants and children out of whom 66\% were neurologically normal\textsuperscript{[13]}.

In our case, presenting as severe congestive heart failure due to left to right shunt through the low resistance vascular bed of the VGAM, caused both pressure and volume overload on the right ventricle. The supra-systemic pulmonary artery pressure was noted only transiently on the first day, the TR was more likely due to the dilatation of the valvular ring. There was improvement in the heart size after appropriate cardiac failure management within a week. At this time no pulmonary hypertension was noted. Persistent Pulmonary Hypertension of the Newborn (PPHN), indicates a more guarded prognosis and may sometimes require treatment with nitric oxide and other advanced modalities\textsuperscript{[14]}.

Among the many ethical dilemmas faced is the proper communication with the parents in an honest and clear manner, based on available knowledge of endovascular management and its outcome. The literature indicates a mean age of five months for endovascular procedures. It is considered that the patient be selectively managed at centers which have the maximum experience in comprehensive management of such rare but nevertheless manageable disorders.

**CONCLUSION**

Neonates presenting with persistent cardiac failure, should be screened for non-cardiac causes, like AV malformation with non-invasive simple technique of transcranial Doppler sonography. Neonatal Cranial Ultrasound by experienced neonatologist can expedite the diagnosis. The recent advances in the interventional endovascular embolization have significantly improved the prognosis of VGAM both in terms of morbidity and mortality.

**ACKNOWLEDGEMENT**

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Case Report

Congenital Chloride Diarrhea Associated with Sensorineural Deafness, and Epilepsy in a Kuwaiti Girl

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ABSTRACT

Congenital chloride diarrhea (CCD) is a rare autosomal recessive disease. It is characterized by persistent, lifelong, watery diarrhea with high fecal chloride concentration, hyponatremia, hypokalemia and hypochloremic metabolic alkalosis. In this report, we describe a nine year old Kuwaiti girl who was diagnosed to have CCD at six months of age, sensorineural deafness at 18 months of age, and epilepsy at 30 months of age. To the best of our knowledge, this appears to be a unique combination that has not been previously reported.

KEY WORDS: chloride co-transporter, congenital chloride diarrhea, epilepsy, sensorineural deafness

INTRODUCTION

Congenital chloride diarrhea (CCD) was first described in 1945 by Gamble et al[1] and Darrow[2], as a congenital watery diarrhea and chronic alkalosis[3]. It has been reported in different ethnic groups from all over the world[4]. Approximately one-third of CCD patients live in Finland, but a high incidence has also been observed in Poland, Saudi Arabia, and Kuwait[5]. In east central Finland, the estimated incidence was 1 in 20,000. In Poland genetic studies have revealed an incidence of 1 per 200,000 live births. Highest frequencies upto 1 in 3200 have been reported among Arab people where parental consanguinity is common; the G187 X mutation is responsible for more than 90% of these cases[6].

CCD results from a defect of the bicarbonate / chloride exchange system in the distal ileum and colon[3]. The defect causes impaired absorption of chloride, acidity of intestinal contents because of impaired excretion of bicarbonate, and secondarily, impaired sodium absorption[7]. Among the main clinical features is chronic, life-threatening watery diarrhea beginning in the prenatal period[8]. Intrauterine diarrhea may lead to polyhydramnios and associated premature birth[9]. Newborns with CCD have distended abdominal girth and lack meconium passage. Hypochloremia and hyponatremia develop rapidly after birth, followed by hypokalemia, hyperbilirubinemia, and metabolic alkalosis secondary to hyper-reninemia and hyperaldosteronemia[3].

The correct diagnosis of CCD can be made when fecal chloride is measured and exceeds 100 mEq/l in stools and also the sum of the Na+ and K+ concentrations. Early diagnosis is essential as hyponatremic episodes in infancy may result in mental and psychomotor impairment[6]. The aim of treatment is to maintain a normal fluid and electrolyte balance, normal blood pH and the presence of slight chloriduria, which is achieved simply by continuous supplementation to replace the diarrhea loss of water, chloride, sodium and potassium. Sodium chloride and potassium chloride should be given intravenously in the early neonatal period and later a solution can be taken orally with a meal[9].

Epilepsy is a heterogeneous disorder defined by recurrent unprovoked seizures affecting about 1 - 3% of the population during their lifetimes[11]. Symptoms vary widely, depending on the region and extent of the brain that participates in the abnormal electrical activity[12].

Hearing process starts by sound vibrations causing sensory neurons in the cochlea (called hair cells) to depolarize repetitively and release their neurotransmitter[13]. Sensorineural deafness is caused by degeneration of the hair cells[13].

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We report this case of a nine year old Kuwaiti girl who had an association of CCD, sensorineural deafness, and epilepsy.

CASE REPORT

This nine year old Kuwaiti girl was born as the first child of first cousin parents having three other sons and two daughters. Only this daughter had CCD. She was delivered after 38 weeks gestation by normal delivery. Her birth weight was 2,000 g. Since birth she was noticed to have watery diarrhea for which, she was admitted to the hospital repeatedly with vomiting and failure to gain weight. Her stool remained watery and increased in frequency to up to seven times per day. Her length and weight were below the third percentile for age. Systemic examination including the nervous system was normal. Laboratory tests showed serum sodium 124 mmol/l, serum chloride 95 mmol/l, serum potassium 2.4 mmol/l, and metabolic alkalosis (serum bicarbonate 36 mmol/l). Sweat test was normal. Urine analysis was normal. Fecal chloride concentration was 117 mmol/l, sodium 20 mmol/l, and potassium 77 mmol/l, fulfilling the two diagnostic criteria of CCD (fecal chloride content > 90 mmol/l and fecal cationic gap F - Na⁺ + K⁺ < Cl⁻). Supplementation of potassium chloride and sodium chloride was initiated with a beneficial effect on weight gain. At the age of 18 months, she was noted to be not attentive and was not pronouncing a single word. Investigations revealed bilateral sensorineural deafness and hearing aids were required.

By 30 months age, she started to have recurrent focal convulsions with secondary generalization in the form of startling look, blinking of eyelids and head noding with loss of consciousness. They were occurring about once weekly and could be finally controlled on valproic acid and clonazepam. Electro-encephalogram showed abnormal background activity with left fronto-centro-temporal focus. Computed tomography (CT) of the brain was normal.

Her sister now aged four years was delivered after 36 weeks gestation with polyhydramnios. Her birth weight was 2100 g. She was admitted to neonatal unit with mild dehydration and abdominal distention. Because her sister had already been diagnosed to have CCD, she was investigated and found to have high fecal chloride excretion with serum electrolytes disturbance compatible with CCD. There was no history of deafness or epilepsy.

DISCUSSION

CCD should be considered as a differential diagnosis to congenital watery diarrhea, since early diagnosis and appropriate treatment are mandatory for the normal development of the child, avoiding severe complications such as neurological sequelae and even death[14].

The basic defect in CCD is the impairment of chloride / bicarbonate exchange in an otherwise normal distal ileum and colon[15]. Active chloride re-absorption is defective. Due to absence of bicarbonate, the intestinal contents become acidic. Consequently, sodium absorption is inhibited and potassium secretion increases. This leads to a significant loss of chloride accompanied by a loss of sodium and potassium, which results in osmotic diarrhea, severe dehydration and hypochloremic alkalosis with hypokalemia[9]. There is no need to over substitute patients with CCD because diarrhea and incontinence greatly reduce their quality of life. Monitoring hydration, electrolyte balance, pH, and excretions of chloride in urine provide variable information on electrolyte balance in these patients. Furthermore, families should be provided with detailed instructions for additional substitutions and / or contact their pediatrician during intercurrent infections disease or episodes of vomiting[8].

CCD gene, also referred to as the down-regulated in adenoma (DRA) gene, is localized on chromosome 7q 31 proximally to the CFTR (cystic fibrosis transmembrane conductance regulator). CCD is caused by mutations in a gene which encodes on intestinal anion transporter. The DRA gene is localized to the most critical region functionally and positionally, encoding a transmembrane protein belonging to the sulfate transporter family[10]. Further studies of the gene structure of CCD will enable the development of primes suitable for amplification of each axon of the gene. These primers enable fast and easy mutation screening and diagnostic testing for CCD[8].

CCD is characterized by loss of chloride co-transporters and diarrhea[16]. Chloride co-transporters play important role in the regulation of cytoplasmic ion concentrations and cell volume as well as in salt transport across epithelia. Chloride co-transporters are expressed in brain, epithelia and other tissues. Loss of chloride co-transporters showed a progressive neurodegeneration in the peripheral and central nervous system and reduced seizure threshold with spike-wave complexes on electrocorticogram in mice[17].

When the intracellular chloride concentration in neurons decreases, it switches its effect from excitatory to inhibitory[18]. Seizures can be generated in response to a loss of balance between excitatory and inhibitory influences and can take the form of either tonic depolarizations or repetitive, rhythmic burst discharges[19].

Chloride co-transporters play a major role in transepithelial chloride and fluid transport.
in marginal cells of the inner ear thus playing a critical role in hearing\cite{20}. Mice lacking chloride co-transporters are deaf because their cells degenerate rapidly after the beginning of hearing\cite{13}.

**CONCLUSION**

Early accurate diagnosis of CCD and early adequate treatment is associated with excellent prognosis and prevention of complications. The relation between low intracellular chloride, loss of chloride co-transporters, deafness, and seizures are not well established in human. Further studies in this aspect are needed to establish the correlation.

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Intra-operative Patient-Controlled Sedation (PCS): Propofol Versus Midazolam Supplementation During Epidural Analgesia (Clinical and Hormonal Study)

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This study was done on sixty adult males scheduled to have an epidural analgesia for elective inguinal hernia repair. The study was designed to compare propofol and midazolam with regard to their suitability for the patient-controlled sedation (PCS) technique during epidural analgesia. Patients were divided into three equal groups and premedicated with 0.2mg.kg-1 oral midazolam. Group I (G1) served as control. Using PCS technique, the pump was programmed to deliver on demand a bolus dose of 0.5 mg.kg-1 of propofol in Group II (G2) or 0.1mg.kg-1midazolam in Group III(G3). Patient’s sedation status was assessed by sedation score, comfort scale and by psychometric testing. The total delivered dose of each tested drug was calculated. Serum concentrations of propofol and midazolam, plasma cortisol and free fatty acids were measured. Propofol and midazolam PCS technique produced excellent and easily controllable sedation. The dose needed to produce steady state sedation was 2.8±1.42 and 0.11±0.6 mg.kg-1.h-1 for propofol and midazolam respectively. Propofol was more suitable than midazolam for PCS because of its rapid onset, favorable recovery profile and low side effects. PCS proved to be a stress-free and acceptable technique.

Voluntary Turnover among Nurses Working in Kuwaiti Hospitals

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Background: Voluntary turnover rates are high among staff nurses working in Kuwaiti hospitals. It is a major problem, costly and it is presumed to impact on the quality of nursing care delivered.

Aims: The two aims of this study were to (1) find out if nurses’ resignations in Kuwaiti hospitals could be ascribed to failure in the recruitment process and (2) examine the feelings of nurses who resigned.

Methods: Two sets of exit interviews with 60 nurses who had resigned were conducted.

Results: No evidence emerged that any false information or misleading information was provided except for the salary adjustments. The real insight lay in what might not have been said in the recruitment interviews. While feelings of discontent emerged in the interviews relating to the loss of income, the greatest source of complaint related to the failure of managers to solve the evident problems.

Conclusions: High rates of voluntary turnover require more attention from administrators and policy makers because of its potential consequences in terms of the quality of nursing care delivered.

Implications for nursing management This paper identifies many causes of nurses’ voluntary turnover. It also shows the need for nursing managers to explore these causes and suggests successful strategies for recruitment and retention practices and policies.
The Importance of Determining the Aggressiveness of Prostate Cancer Using Serum and Tissue Molecular Markers

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Incidental prostate cancer (PCa) has been demonstrated at autopsy in about 80% of men aged 80 years and above and also in 10%-15% of younger men aged 30-50 years in the United States. These data imply a wide variation in aggressiveness of prostate cancer, from indolent tumors to aggressive cancers that kill the patients. The use of prostate specific antigen (PSA) in screening for PCa may detect even indolent disease for which radical prostatectomy may not be necessary. Currently available criteria such as histological grade, PSA level, stage of the disease do not always predict outcome. Furthermore, only about 80% of men with metastatic PCa will respond to first line hormone manipulation and once the patient develops hormone resistant prostate cancer (HRPCa), survival remains poor. Recent genomic and proteomic studies have provided many novel molecular markers that may help to redefine prognostic parameters. This paper is a review of studies using these novel markers in order to determine whether prostate cancer patients with the following characteristics have more aggressive cancer than those without: a) high serum levels of cathepsin B, survivin, Her - 2 / neu, IGFBP-2; b) low serum stefin A, IGFBP-3, c) positive immuno-staining of primary tumors for Her-2/neu, survivin and cathepsin B / stefin A ratio > 1 and d) gene expression of AMACR, HER-2/neu, high Bcl-2: Bax ratio and EZH2 in cancer cells. These markers have been chosen for review because they are among the most promising markers emerging currently.

Salmonella Enterica Serotype Typhi in Kuwait and its Reduced Susceptibility to Ciprofloxacin

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Salmonella enterica serotype typhi continues to be an important public health problem in Kuwait. Analysis of the isolates from 163 patients, collected between 1995 and 2003, showed that the majority were from patients from the Indian sub-continent, including 45 from Bangladesh, 38 from India and 30 from Pakistan. Fifty-four of the strains showed multiple antibiotic resistance (MDR). Twenty-five strains were from Kuwaitis, with 15 aged <18 years. Bacteriophage typing of 20 isolates from Kuwaitis revealed that they belonged to 8 different phage types, and that the 3 MDR strains were phage type E1. Random amplified polymorphic DNA typing showed genetic variability amongst isolates from Kuwaiti patients. This method conveniently demonstrated the identity of 4 isolates associated with a small outbreak. 48 isolates from 2002-3 were tested for reduced susceptibility to quinolones. 12 of 18 MDR strains and 7/30 susceptible strains showed reduced susceptibility to ciprofloxacin (minimum inhibitory concentration 0.125-0.5 mg/L). All 12 strains were tested for mutation in the quinolone resistance determining region (QRDR) of the gyr A gene. The mutation ser83 phe was detected in the 10 strains tested. Thus typhoid fever in Kuwait is predominantly associated with those who have traveled from endemic areas to work in Kuwait. The incidence of MDR strains remains at about 30%. Reduced susceptibility to ciprofloxacin in MDR S. typhi has increased from (11%) in 1995-1996 to (67%) in 2002-2003 and from (0%) to (23%) in susceptible strains. Mutation of the gyrA gene is the mechanism most often responsible.
Treatment of Renal Calculi by Lithotripsy: Minimizing Short-Term Shock Wave Induced Renal Damage by Using Antioxidants


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Treatment with extracorporeal shock wave lithotripsy (ESWL), the preferred method of treating kidney stones <3 cm in size, has been shown to induce silent and often self-limiting acute and chronic lesions in the kidneys and adjacent organs. We conducted a randomized clinical trial to determine whether ESWL produces ischaemia and reperfusion injury in the kidneys and whether oral administration of antioxidants reduces the degree of short-term renal injury in patients treated with ESWL. The study included 120 patients with renal stones (1-3 cm in size) treated with ESWL. The patients were divided into three groups—patients in group A (n=39) served as a control group and were not given any antioxidants; patients in group B (n=41) were given two capsules of antioxidants “Nature Made R: “ 2 h before ESWL, and 2 and 8 h after ESWL; and patients in group C (n=40) were given two capsules of the antioxidants 2 and 8 h after ESWL. Double ‘J’ stents were inserted in patients before treatment with ESWL. Blood and urine samples were obtained from all patients just before the start of treatment with ESWL, and at 2 and 24 h and on 7th and 28th day after ESWL. Serum levels of malondialdehyde (MDA), alpha-tocopherol, cholesterol, albumin and ascorbic acid, and alpha-tocopherol/cholesterol ratio were determined. Urinary levels of albumin and beta(2) microglobulin were also determined as measures of renal tubular injury. At 24 h after ESWL, patients given antioxidants (groups B + C) had significantly reduced mean serum concentration of MDA (P<0.001); higher levels of serum ascorbic acid (P<0.001) and serum albumin (P<0.001); lower alpha-tocopherol/cholesterol ratio, lower urinary albumin and beta(2) microglobulin levels compared with patients who did not receive antioxidants (group A). These findings suggest that treatment with ESWL generates free radicals through ischaemic/reperfusion injury mechanism, and that oral administration of antioxidant may protect these patients from short term renal injury caused by ESWL.

Seasonality in Pulmonary Tuberculosis among Migrant Workers Entering Kuwait

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Background: There is paucity of data on seasonal variation in pulmonary tuberculosis (TB) in developing countries contrary to recognized seasonality in the TB notification in western societies. This study examined the seasonal pattern in TB diagnosis among migrant workers from developing countries entering Kuwait.

Methods: Monthly aggregates of TB diagnosis results for consecutive migrants tested between January 1, 1997 and December 31, 2006 were analyzed. We assessed the amplitude (alpha) of the sinusoidal oscillation and the time at which maximum (theta degrees ) TB cases were detected using Edwards’ test. The adequacy of the hypothesized sinusoidal curve was assessed by chi2 goodness-of-fit test.

Results: During the 10 year study period, the proportion (per 100,000) of pulmonary TB cases among the migrants was 198 (4608/2328582), (95% confidence interval: 192 - 204). The adjusted mean monthly number of pulmonary TB cases was 384. Based on the observed seasonal pattern in the data, the maximum number of TB cases was expected during the last week of April (theta degrees = 112 degrees ; P < 0.001).
The amplitude (+/- se) (alpha = 0.204 +/- 0.04) of simple harmonic curve showed 20.4% difference from the mean to maximum TB cases. The peak to low ratio of adjusted number of TB cases was 1.51 (95% CI: 1.39 - 1.65). The chi2 goodness-of-test revealed that there was no significant (P > 0.1) departure of observed frequencies from the fitted simple harmonic curve. Seasonal component explained 55% of the total variation in the proportions of TB cases (100,000) among the migrants.

Conclusion: This regularity of peak seasonality in TB case detection may prove useful to institute measures that warrant a better attendance of migrants. Public health authorities may consider reallocation of resources in the period of peak seasonality to minimize the risk of Mycobacterium tuberculosis infection to close contacts in this and comparable settings in the region having similar influx of immigrants from high TB burden countries. Epidemiological surveillance for the TB risk in the migrants in subsequent years and required chemotherapy of detected cases may contribute in global efforts to control this public health menace.

Primary Immunodeficiency Disorders: Survey of Pediatricians in Kuwait


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Introduction: Early diagnosis of primary immunodeficiency disorders (PID) is critical so life saving interventions can be implemented to avoid significant morbidity and mortality. Unfortunately, they are frequently misdiagnosed, which results into significant delay in diagnosis. This study aimed to determine the knowledge and practice of pediatricians in Kuwait about PID.

Materials and methods: A 66-item self-administered questionnaire was designed and distributed to the pediatricians working at all six governmental hospitals to measure their knowledge and practice about PID. A total of 244 pediatricians (78.4%; 143 males and 101 females) participated in the study. The mean age of participants was 40 years, and the mean number of years working in pediatrics was 13 years. The mean overall score was 59.6%, whereas the mean score in clinical presentation section was 63%, in associated diseases and syndromes section 58%, and in laboratory investigations section 51%. Only 26% of the participants answered correctly at least 2/3 of the questions (67% of the questions).

Conclusion: This survey demonstrates that there is universal deficiency in both the knowledge and practice of pediatricians in the field of PID. Implementation of strategies to improve the awareness of pediatricians about PID is critical so early therapeutic interventions can be done to improve the health and prevent morbidity and mortality.

Depressed Patients’ Preferences for Education about Medications by Pharmacists in Kuwait

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Objective: To assess patients’ opinion toward receiving written or specialized verbal pharmacists’ interventions and to determine the effect of these interventions on patients’ medication knowledge.

Methods: 150 newly diagnosed patients with unipolar depression and initiated with a single antidepressant were randomized into 3 groups: control, leaflet and counselling, and interviewed at initiation and after 6-8 weeks of treatment at the outpatient department of the Psychiatric Hospital in Kuwait.

Results: 50% of respondents asserted that clinicians did not give them sufficient information while 90%
favoured the idea of receiving further information about therapy. Forty seven percent of participants failed to return for the second follow-up appointment. The drop-out rate was 66% in the control, 42% in the Leaflet and only 34% in the counselling groups (P=0.004). A broad support for receiving leaflets and drug counselling (97%) was found among attendees. Moreover, 94% of the counselling and 79% of the leaflets group affirmed that they received adequate information compared to 47% of the control (P=0.001). Counselling was found to be significantly associated with a much higher recall of medicine name (OR=9.6, P=0.01), how to manage missed doses (OR=8.9, P=0.007), and correct use of medication (OR=31.3, P<0.001). Leaflet use was less strongly associated than counselling and was statistically significant for recall regarding correct use of medication (OR=8.4, P=0.009).

**Conclusion:** Pharmacists in a psychiatric institution can play an important role in satisfying patient demands for specialized information about their medications. Patients with depression appear very eager to receive additional drug information with modest difference between the written and the verbal counselling interventions. Patients looked at the two interventions in a very positive manner and no difference was observed between patients in the leaflets and in the counselling group with regards to how helpful, sufficient, supportive and reassuring was the educational material. However, both interventions were more informative than the control in conveying elemental drug information to patients.

**Practice implications:** In contrast with the lack of enthusiasm that some clinicians express, the affirmativeness that was expressed by patients towards receiving written or verbal specialized educational interventions by pharmacists may support the psychiatric hospital pharmacists’ stands in providing them for all patients which may aid in improving patients compliance and probably treatment outcome.

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**Butyrylcholinesterase Activity and Lymphocyte Subpopulations in Peripheral Blood of Kuwaiti Women Experiencing Recurrent Spontaneous Abortion**

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*J Reprod Immunol* 2008; 77:186-194

This study has evaluated the hypothesis that activity of the detoxifying enzyme butyrylcholinesterase (BuChE) correlates with levels of serum anti-cardiolipin antibodies (ACA) and T lymphocytes in peripheral blood of women experiencing recurrent spontaneous abortion (RSA). Peripheral venous blood from 16 non-pregnant, RSA-afflicted women and 8 healthy non-pregnant women was analyzed for frequency of T lymphocyte subpopulations by two-color flow cytometry and for serum BuChE using butyrylthiocholine iodide/spectrophotometry. RSA-afflicted women with high serum ACA, but not those with normal ACA levels, exhibited significantly increased percentages of CD4+CD25+ cells (p<0.01) and CD4+HLA-DR+ cells (p<0.05) relative to healthy women. CD4+CD25+(high) cells were significantly lower (p<0.05), while CD4+CD25+(low) cells were significantly higher (p<0.01), in women with elevated ACA compared to healthy women and to RSA women with normal ACA. Relative to healthy, non-pregnant subjects, serum BuChE activity in RSA patients was elevated, both for those with normal ACA (p<0.001) and elevated ACA levels (p<0.01). Among healthy controls, a significant positive correlation was observed between frequency of CD3+NK cells and BuChE activity (p<0.01), but not for RSA-afflicted subjects. A positive correlation between BuChE activity and frequency of CD4+CD25+ cells, as well as CD4+CD25+(high) cells, was observed in the RSA-afflicted subject group with elevated ACA (p<0.05), which may be related to induction of BuChE by toxic metabolites resulting from pathogenic T cell activity. It is concluded that, among RSA patients, high serum ACA correlates with elevated levels of activated T cells and reduced CD4+CD25+(high)/CD4+CD25+(low) cells in comparison to healthy women or those afflicted with RSA but with normal ACA. BuChE activity is observed to be elevated in RSA patients irrespective of serum ACA status.
Benthic Foraminifera from Polluted Marine Environment of Sulaibikhat Bay (Kuwait)

Al-Zamel AZ, Al-Sarawi MA, Khader SR, Al-Rifaiy IA

Department of Earth & Environmental Sciences, Faculty of Science, Kuwait University, P.O.B 5969, Safat, 13060, Kuwait, E-mail: abzamil@kuc01.kuniv.edu.kw

Environmental Monitoring and Assessment 2008 Mar 26 [Epub ahead of print]

Quantitative analyses of recent benthic foraminiferal assemblages (living and dead) were carried out on the surface sediments of Sulaibikhat Bay. Marked contrast in foraminiferal assemblages between the shallow tidal mudflats and the deep tidal channel and their relation to the extent of pollution were observed. Cluster analysis of quantitative data on the distribution of foraminiferal tests revealed three assemblages that depend mainly on the intensity of pollution; (1) a highly polluted tidal flat assemblage, (2) normal (or less polluted) mud flat assemblage and, (3) tidal channel and subtidal assemblage. The highly polluted assemblage characterized by a drop in species densities (<100 tests/20 cm(3) sediment) but with high average diversity (5.8 Yule-Simpson Index). The microfauna of the less polluted flat displays relatively lower diversity (4.6) but high density of tests (47.2% of the total picked tests). The most abundant species of this assemblage is Ammonia tepida, displays its maximum density in this assemblage. Ammonia tepida drops in density from 17.12% to 3.07% in the polluted assemblage. Tidal channel foraminiferal assemblages should normally display lower diversities than those of tidal flats, because tidal current in the channels tend to wash away most nutrient materials. However, this is not the case of the present study area which could be due to environmental setting of the Sulaibikhat Bay in which tidal currents bring in exceptionally high amounts of nutrients from Shatt Al-Arab Estuary and in which the tidal flats are strongly and adversely polluted.

Species Spectrum of Nontuberculous Mycobacteria Isolated from Clinical Specimens in Kuwait

Mokaddas E, Ahmad S

Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait

Current Microbiology 2008; 56:413-417

Specific identification of mycobacteria is of clinical relevance since treatment varies according to the Mycobacterium species causing infection. All mycobacterial isolates are currently identified as M. tuberculosis (MTB) or nontuberculous mycobacteria (NTM) based on p-nitro-alpha-acetylamino-beta-hydroxypropiophenone (NAP) test, and the species spectrum of NTM-causing infections in Kuwait remains unknown. This study identified all NTM strains isolated in Kuwait from 1 October 2003 to 31 March 2004 to the species level. The mycobacteria were cultured from various clinical specimens using the BACTEC 460 TB system and NAP test was performed to differentiate MTB from NTM strains. The INNO-LiPA MYCOBACTERIA v2 assay (LiPA) was used for species-specific identification of NTM strains and some randomly selected MTB strains. The LiPA results for selected isolates were confirmed by DNA sequencing of the 16S-23S internal transcribed spacer region. A total of 325 isolates of Mycobacterium species originating from 305 individual patients were recovered during the study period, with 307 and 18 isolates identified as MTB and NTM, respectively. The LiPA correctly identified all 18 MTB isolates analyzed. Seven different NTM species were identified among 18 NTM isolates originating from 14 patients, with M. fortuitum causing the majority of NTM infections in Kuwait. One patient was infected with two NTM species. Rapid species-specific identification of NTM may help with appropriate treatment regimens for proper patient management.
Forthcoming Conferences and Meetings

Compiled and edited by

Babichan K Chandy

Kuwait Medical Journal 2008, 40 (3): 257-262

6th International Congress on Autoimmunity
Sep 03-07, 2008
Porto, Portugal
Contact: Jo Jackson
Tel: 41-229-080-488; Fax: 41-227-322-850
E-Mail: autoimmunity@kenes.com

Intraoperative Echocardiography in the 21st Century
Sep 04-07, 2008
Atlanta, GA, United States
Contact: Continuing Medical Education, 1462 Clifton Road, Suite 276 Atlanta, GA 30322
Tel: 1-888-727-5695 / 404-727-5695; Fax: 404-727-5667
E-Mail: cme@emory.edu

ILCA 2008
Sep 05-07, 2008
Chicago, IL, United States
Contact: Cecilia Waldvogel
Tel: 322-789-2345; Fax: 322-743-1550
E-Mail: info@ilca-online.org

Organ Imaging Review 2008
Sep 07-10, 2008
Toronto, ON, Canada
Contact: Office of Continuing Education & Professional Development
Tel: 416-978-2719; Fax: 416-946-7028
E-Mail: help-MIM0802@cmetoronto.ca

STD 7 / Aids 3
Sep 07-10, 2008
Goiânia, Brazil
Contact: Alberto Tiburcio
Tel: 69-32-223-153
E-Mail: josesarahoscar@ibest.com.br

14th World Congress of Psychophysiology
Sep 08-13, 2008
St.Petersburg, Russia
Contact: Dr.Tatiana Denisenko
Tel: 812-335-2055 ext 160; Fax: 812-335-2039
E-Mail:Tatiana.Denisenko@monomax.org

Dermatopathology Conference
Sep 10, 2008
Sioux Falls, SD, United States
Contact: Office of Continuing Medical Education,
Sanford School of Medicine, 1400 W. 22nd St., Rm 117, Sioux Falls, SD 57105 Tel:605-357-1488; Fax:605-357-1488
E-Mail: cme@usd.edu

5th International Pediatric Intestinal Failure and Rehabilitation Symposium
Sep 11-13, 2008
Pittsburgh, PA, United States
Contact: Jada Shirriel
Tel: 412-647-8216; Fax: 412-647-8222 / 412-647-1244
E-Mail: shirrielj@upmc.edu

19th Annual Coronary Interventions
Sep 17-19, 2008
San Diego, CA, United States
Contact: Gretchen Ploen
Tel: 858-587-4404; Fax: 858-587-4438
E-Mail: Med.edu@scrippshealth.or

20th Australasian Society for HIV Medicine Conference
Sep 17-20, 2008
Perth, WA, Australia
Contact: Daliah Frank
Tel: 61-282-040-770; Fax: 61-292-124-670
E-Mail: conferenceinfo@ashm.org.au

Peripheral T-Cell Lymphoma Forum
Sep 18-20, 2008
Washington, DC, United States
Contact: Damaris Cruz
Tel: 201-594-0400; Fax: 201-594-0409
E-Mail: dcruz@jwoodassoc.com

Management of Chronic Kidney Disease
Sep 22-25, 2008
Coventry, England, United Kingdom
Contact: Dr Charlotte Moonan
Tel: 024-76-523-540; Fax: 024-76-523-701
E-Mail: Charlotte.Moonan@warwick.ac.uk

6th World Stroke Congress
Sep 24-27, 2008
Vienna, Austria
Contact: Ms. Rina Kinris
Tel: 41-229-080-488; Fax: 41-227-322-850
E-Mail: stroke2008@kenes.com
Forthcoming Conferences and Meetings

September 2008

**Paediatric Gastroenterology** Course
Sep 25-27, 2008
Valletta, Malta
Contact: Dr. Chris Fearne
Tel: 00-35-679-707-209
E-Mail: christopher.fearne@gov.mt

2008 *Gastrointestinal Oncology* Conference
Sep 25-27, 2008
Arlington, VA, United States
Contact: Conference Secretariat: International Society of Gastrointestinal Oncology, Mr. Robert Ross, 200 Broadhollow RD, 11747 Melville
Tel: 1-631-390-8390; Fax: 1-631-393-5091
E-Mail: email@isgio.org

The Changing Practice of *Anesthesia*
Sep 25-28, 2008
San Francisco, CA, United States
Contact: UCSF Office of Continuing Medical Education, 3333 California Street, Room 450, San Francisco, CA 9411 Tel: 415-476-4251 / 415-476-5808; Fax:415-476-0318 / 415-502-1795
E-Mail:info@ocme.ucsf.edu

European Conference on *Paediatric Anaesthesia*
Sep 25-27, 2008
Athens, Greece
Contact: Aktina City Congress S.A.
Tel: 302-103-232-433; Fax: 302-103-232-338
E-Mail: feapa2008@qaktinacitycongress.com

6th Annual World Congress on *Insulin Resistance Syndrome*
Sep 25-27, 2008
Los Angeles, CA, United States
Contact: Nava Mekel
Tel: 818-342-1889; Fax: 818-342-1538
E-Mail: insulinresistance@pacbell.net

ISN Nexus symposium on *Transplantation and the Kidney*
Sep 25-28, 2008
Rome, Italy
Contact: Michael Podt
E-Mail: michael.podt@isn-online.org

6th Advanced Symposium on *Congenital Heart Disease in the Adult*
Sep 26-27, 2008
Thessaloniki, Greece
Contact: Ms Artemis Thoma
Tel: 00-302-310-265-898; Fax: 00-302-310-240-669
E-Mail: thesis@thesis-pr.com

**Ophthalmic Anesthesia** Society (OAS) 22nd Annual Meeting
Sep 26-28, 2008
Chicago, IL, United States
Contact: Karen S. MORGAN
Tel: 1-805-534-0300; Fax: 1-805-534-9030
E-Mail: info@eyeanesthesia.org

**Practical Office Dermatology**
Sep 26-27, 2008
Albuquerque, NM, United States
Contact: University of New Mexico School of Medicine, Office of Continuing Medical Education, MSC09 5370, 1 University of New Mexico, Albuquerque, New Mexico 87131-0001 Tel: 505-272-3942; Fax:505-272-8604
E-Mail: CMEWeb@salud.unm.edu

13th International Congress on *Hormonal Steroids and Hormones & Cancer*
Sep 27-30, 2008
Quebec City, QC, Canada
Contact: Secretariat
Tel: 418-654-2704; Fax: 418-654-2735
E-Mail: info@ichshc2008.com

40th Congress of the International Society of *Paedriatic Oncology*
Oct 01-06, 2008
Berlin, Germany
Contact: Conference Secretariat: SIOP 2008 Secretariat, c/o MCI Berlin Office, Ines Paschen, Markgrafenstrasse 56, 10117 Berlin
Tel: 49-30-204-590; Fax: 49-30-204-950
E-Mail: siop2008@cpb.de

Perspectives in *Melanoma XII*
Oct 02-04, 2008
Scheveningen, Netherlands
Contact: Customer Service, Tel:770-751-7332; Fax:770-751-7334
E-Mail: meetings@imedex.com

4th World Congress on Quality in *Medical Practice*
Oct 02-05, 2008
Thessaloniki, Greece
Contact: Psirropoulos Dimitrios Z, MD, PhD
Tel: 00-302-310-963-286; Fax: 00-302-310-963-288
E-Mail: cardio.gennim.thess@mail.gr

**Ultrasonography** for Nephrologists
Oct 03-05, 2008
Atlanta, GA, United States
Contact: Continuing Medical Education, 1462 Clifton Road, Suite 276 Atlanta, GA 30322
Tel: 1-888-727-5695 / 404-727-5695; Fax: 404-727-5667
E-Mail: cme@emory.edu
2nd Mediterranean Clinical Immunology Meeting
Oct 04-07, 2008
Antalya, Turkey
Contact: Mrs. Ayse Askin-Erten
Tel: 902-122-823-373; Fax: 902-122-823-321
E-Mail: immunology@serenas.com.tr

Chest imaging 2008
Oct 05-07, 2008
Boston, MA, United States
Contact: Harvard Medical School CME Office
Tel: 617-384-8600; Fax: 617-384-8686
E-Mail: hms-cme@hms.harvard.edu

National Cancer Research Institute Conference 2008
Oct 05-08, 2008
Birmingham, England, United Kingdom
Contact: Conference Secretariat: NCRI Conference Secretariat Ms Sharon Vanloo, P.O. Box 49709 61 Lincoln’s Inn Fields, WC2A 3 London
Tel: 44-2-0-72-693-420; Fax: 44-2-0-70-616-004
E-Mail: ncriconference@ncri.org.uk

5th World Congress of the European Club for Paediatric Burns
Oct 08-11, 2008
Gdansk, Poland
Contact: Wyrzykowski Dariusz
Tel: 48-601-685-379; Fax: 00-48-583-026-427
E-Mail: pedsurg@amg.gda.pl

Acute Care Psychiatry Clinical Review
Oct 09-11, 2008
Chicago, IL, United States
Contact: Vicki Klein
Tel: 800-323-2688; Fax: 507-284-0532
E-Mail: cme@mayo.edu

Laser & Aesthetic Skin Therapy: What’s the Truth
Oct 10-12, 2008
Boston, MA, United States
Contact:CME Office Tel: 617-384-8600; Fax:617-384-8686
E-Mail: hms-cme@hms.harvard.edu

Rheumatology & Cardiovascular Medicine
Oct 11-25, 2008
Istanbul, Turkey
Contact: Dr. Martin Gerretsen
Tel: 1-888-647-7327; Fax: 1-888-547-7337
E-Mail: cruises@seacourses.com

10th Annual Congress of Turkish Society of Internal Medicine
Antalya, Turkey
Contact: Hakan BIYIKLI Tel: 903-124-405-011; Fax:903-124-414-563
E-Mail: hakan.biyikli@serenas.com.tr

2008 Cardiometabolic Health Congress
Oct 15-18, 2008
Boston, MA, United States
Contact: Dina Kouveliotes
Tel: 877-571-4700; Fax: 866-218-9168
E-Mail: dk@cardiometabolichealth.org

International Congress of Pediatric Hepatology, Gastroenterology and Nutrition (11th)
Oct 15-18, 2008
Sharm El-Sheikh, Egypt
Contact: Professor Mortada El-Shabrawi, MD
Tel: 20-123-133-705; Fax: 20-237-619-012
E-Mail: melshabrawi@kasralainy.edu.eg

Obstetric Anaesthesia Continuing Medical Education Meeting
Oct 16-17, 2008
Blenheim, New Zealand
Contact: Juliette Mullumby Tel:61-395-106-299; Fax:61-395-106-786
E-Mail: jmullumby@anzca.edu.au

10th International Anesthesia, Pain and Intensive Care Conference
Oct16-19, 2008
Rawalpindi, Pakistan
Contact:Shahab Naqvi Tel: 00-92-519-272-928; Fax:00-92-519-271-015
E-Mail: shahab15@hotmail.com

7th Annual Advances in Breast MRI
Oct 16-18, 2008
Las Vegas, NV, United States
Contact: Stanford Radiology CME
Tel: 650-473-5052; Fax: 650-473-5062
E-Mail: radiologycme@med.stanford.edu

Laser Congress Korea 2008
Oct 16-19, 2008
Seoul, Republic of Korea
Contact: Joung OK Lee MD
Tel: 82-25-113-713; Fax: 82-25-173-713
E-Mail: KHG000@UNITEL.CO.KR

8th Symposium on Advances in Cardiac Diseases
Oct 17-18, 2008
Turin, Italy
Contact: Ms Barbara Rossi
Tel: 39-0-10-583-224; Fax: 39-0-105-531-544
E-Mail: acd2008@aristea.com
Mumbai, India
Contact: Dr. R. Madhav Rao Tel: 91-0-2-225-228-966
E-Mail: madhav.1949@gmail.com

6th Australasian Viral Hepatitis Conference
Oct 20-22, 2008
Brisbane, QLD, Australia
Contact: Nicole Robertson
Tel: 61-282-040-770; Fax: 61-292-124-670
E-Mail: conferenceinfo@hepatitis.org.au

XXIV National Cardiology Congress of the Turkish Society of Cardiology
Oct 24-27, 2008
Antalya, Turkey
Contact: Meeting Organiser
E-Mail: tkd@tkd.org.tr

Acute Cardiac Care 2008
Versailles, France
Contact: Meeting Organiser
E-Mail: EuroACCsecretariat@escardio.org

12th Biennial International Gynecologic Cancer Society Meeting
Bangkok, Thailand
Contact: Conference Secretariat: International Gynecologic Cancer Society, PO Box 1726, CH-121 Geneva
Tel: 41-229-080-488; Fax: 41-227-322-850
E-Mail: igcs-11@kenes.com

International Congress on Traditional and Complementary Medicine
Sari Country: United Arab Emirates
Contact: Dr. Gholami Tel:981-513-257-230; Fax:981-513-261-244
E-Mail: ictcm@mazums.ac.ir

Clinical Trials: ICH GCP meeting
Oct 28-29, 2008
Kiev, Ukraine
Contact: Kristina Shevchenko
E-Mail: dr@nbscience.com

Advances in Physiology and Pharmacology in Anesthesia and Critical Care
Nov 02-05, 2008
White Sulphur Springs, WV, United States
Contact: Jan Killmeier Tel:336-716-2712; Fax:336-716-8190
E-Mail: killmeir@wfubmc.edu

5th French-Brazilian Oncology Congress
Nov 06-08, 2008
Rio De Janeiro, Brazil
Contact: Conference Secretariat: Sociedade Franco Brasileira de Oncologia c/o Sucesssevents, Carla Ismael, Avenida Nossa Senhora de Copacabana 1059/601, 22060- Rio de Janeiro
Tel: 55-212-247-7874; Fax: 55-212-247-7874
E-Mail: Vcongresso@sbo.com.br

American College of Allergy, Asthma & Immunology Annual Meeting 2009
Nov 06-11, 2009
Miami Beach, FL, United States
Contact: Meeting Organiser
Tel: 847-427-1294; Fax: 847-427-1200
E-Mail: mail@acaai.org / meetings@acaai.org

Respirology & Surgery Update
Nov 07-17, 2008
San Jose, Costa Rica
Contact: Dr. Martin Gerretsen
Tel: 1-888-647-7327; Fax: 1-888-547-7337
E-Mail: cruises@seacourses.com

Three-day Course on Obstetric Anaesthesia and Analgesia
Nov 10-12, 2008
London, England, United Kingdom
Contact: Meeting Secretariat
Tel: 44-2-087-411-311; Fax: 44-2-087-410-611
E-Mail: www.oaameetings.info

2nd Annual Aids Research Congress of Iran
Nov 12, 2008
Iran
Contact: Amir Sharif, Tel: 00-982-166-918-899

6th International Conference on Pain Control and Regional Anaesthesia
Nov 12-16, 2008
Havana, Cuba
Contact: Jo Watling
Tel: 00-44-1-462-471-801; Fax: 00-44-1-462-452-562
E-Mail: jo.watling@choicelive.com

Asia Pacific Geriatric Conference (APGC) 2008
Nov 13-16, 2008
Bali, Indonesia
Contact: Meeting Organiser
Tel: 62-213-146-633; Fax: 62-2-155-960-179
E-Mail: apgc@pharma-pro.com
The 3rd Iranian Asthma Meeting  
Nov 17-19, 2009  
Tehran, Iran  
Contact: Iranian Society of Asthma & Allergy  
Tel: 982-166-938-545; Fax: 982-166-428-995  
E-Mail: isaacong@tums.ac.ir

Advanced International Training Course in Transplant Coordination  
Nov 24-28, 2008  
Barcelona, Spain  
Contact: Monica Peralta  
Tel: 34-934-037-687; Fax: 34-934-039-920  
E-Mail: mperalta@il3.ub.edu

36th Biennial World Congress of the International College of Surgeons  
Dec 03-06, 2008  
Vienna, Austria  
Contact: stephane dazet  
Tel: 41-223-399-576; Fax: 41-223-399-621  
E-Mail: ics@il3.ub.edu

AAAP 19th Annual Meeting & Symposium  
Dec 04-07, 2008  
Boca Raton, FL, United States  
Contact: AAAP, 345 Blackstone Blvd, 2nd Floor  
RCH, Providence RI 02906  
Tel: 401-524-3076; Fax: 401-272-0922  
E-Mail: information@aaap.org

What’s New in Gastroenterology & Hepatology?  
Dec 05-06, 2008  
Dallas, TX, United States  
Contact: The Office of Continuing Medical Education (CME)  
Tel: 214-648-2166 / 800-688-8678; Fax: 214-648-2317  
E-Mail: cmeregistrations@utsouthwestern.edu

Current Concepts in Ophthalmology  
Dec 05-07, 2008  
West Palm Beach, FL, United States  
Contact: Mayo School of Continuing Medical Education Office  
E-Mail: cme-jax@mayo.edu / cme@mayo.edu

2nd Ditan International Conference on Infectious Diseases  
Nov 14-17, 2008  
Beijing, China  
Contact: Cosoman Limited Tel: 85-228-272-090; Fax:85-228-272-220  
E-Mail: info@cosoman.com

26th Annual Infectious Disease Seminar for the Practicing Physician  
Dec 05-07, 2008  
Naples, OH, United States  
Contact: Julie Embick Phone:800-325-1212; Fax:330-325-5929  
E-Mail: ce@neoucom.edu

The Medical Management of HIV/AIDS  
Dec 11-13, 2008  
San Francisco, CA, United States  
Contact: UCSF Office of Continuing Medical Education, 3333 California Street, Room 450, San Francisco, CA 9411  
Tel: 415-476-4251 / 415-476-5808; Fax: 415-476-0318  
E-Mail: info@ocme.ucsf.edu

International HIV/AIDS Conference titled “Challenges & Insights”  
Dec 15-17, 2008  
London, England, United Kingdom  
Contact: Abubakar Yaro Tel : 447-939-848-695  
E-Mail: abubakar@ahro.kabissa.org

Infectious Diseases in the Adult Patient: A Primary Care Update  
Dec 29, 2008 – Jan 02, 2009  
Sarasota, FL, United States  
Contact: Christy or Cristina Tel:1-866-267-4263 or 1-941-388-1766; Fax:1-941-365-7073  
E-Mail: mail@ams4cme.com

STD Intensive  
Jan 12-16, 2009  
Cincinnati, OH, United States  
Contact: University of Cincinnati, Continuing Medical Education, P.O. Box 670556, Cincinnati, OH 45267-0556 Tel.:1-800-207-9399 / 513-558-7277; Fax:513-558-1708 or 513-558-1756  
E-Mail: uccme@uc.edu

6th International Conference for Medical Students in the GCC Countries  
Jan 18-21, 2009  
Al Ain, United Arab Emirates  
Contact: Dr. Abdulla Al Rahoomi Tel.: 00-971-504-475-142; Fax:00-97-137-137-392  
E-Mail: gcc6mconf@uaeu.ac.ae

Dermatology, Lower Extremity, and Practice Management  
Jan 18-Feb 01, 2009  
Santiago, Chile  
Contact: Dr. Martin Gerretsen  
Tel: 1-888-647-7327; Fax: 1-888-547-7337  
E-Mail: cruises@seacourses.com
Forthcoming Conferences and Meetings
September 2008

New Horizons in Anesthesiology
Feb 08-13, 2009
Steamboat Springs, CO, United States
Contact: Office of Continuing Medical Education
Tel: 404-727-5695; Fax: 404-727-5667
E-Mail: cme@emory.edu

The 7th International Congress of the Egyptian Society of Pediatric Allergy and Immunology (ESPAI 2009)
Feb 18-19, 2009
Cairo, Egypt
Contact: Prof. Yehia El-Gamal (President of the Congress) Tel: 20-233-471-000; Fax:20-233-045-060
E-Mail: congress@espai-eg.org

STD Advanced
Feb 23-27, 2009
Cincinnati, OH, United States
Contact: University of Cincinnati, Continuing Medical Education, P.O. Box 670556, Cincinnati, OH 45267-0556 Tel: 1-800-207-9399 / 513-558-7277; Fax:513-558-1708 or 513-558-1756
E-Mail: uccme@uc.edu

Emergency Medicine: An Evidence-Based Approach to Adult Care
Feb 23-27, 2009
Sarasota, FL, United States
Contact: Christy or Cristina Tel: 1-866-267-4263 or 1-941-388-1766; Fax:1-941-365-7073
E-Mail: mail@ams4cme.com

International Symposium on Antimicrobial Agents and Resistance (ISAAR 2009)
Mar 18-20, 2009
Bangkok, Thailand
Contact: Susan Chung Tel: 822-3410-0327; Fax:822-3410-0023
E-Mail: isaar@ansorp.org

Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings
Mar 23-27, 2009
Sarasota, FL, United States
Contact: Christy or Cristina Tel: 1-866-267-4263 or 1-941-388-1766; Fax:1-941-365-7073
E-Mail: mail@ams4cme.com

24th Annual New Treatments in Chronic Liver Disease
Apr 04-05, 2009
San Diego, CA, United States
Contact: Meredith Insch
Tel: 858-587-4404; Fax: 858-587-4438
E-Mail: Med.edu@scrippshealth.org

8th Congress of European Federation of Internal Medicine
May 27-30, 2009
Istanbul, Turkey
Contact: Hakan BIYIKLI Tel: 903-124-405-011; Fax:903-124-414-563
E-Mail: hakan.biyikli@serenas.com.tr

23rd International Conference of the European Society for Philosophy of Medicine and Healthcare
Aug 19-22, 2009
Tubingen, Germany
Contact: Dr. Bert Gordijn, Secretary of the ESPMH, Dept. of Ethics, Philosophy and History of Medicine, Radboud University Nijmegen Medical Centre, P.O.Box: 9101, 6500 HB Nijmegen, The Netherlands
E-mail: b.gordijn@efg.umcn.nl

The 4th International Congress on Pulmonary Diseases, Intensive Care and Tuberculosis
Oct 12-15, 2009
Tehran, Iran
Contact: Maliheh Bitaraf Tel: 982-120-109-507; Fax: 982-120-109-484
E-Mail: fic@nritld.ac.ir
WHO-Facts Sheet

1. New Checklist to Help make Surgery Safer
2. Two and Half Billion Live with Poor Sanitation Facilities
3. Noncommunicable Diseases now World’s Biggest Killers
4. New Rapid Tests for Drug-Resistant TB for Developing Countries

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2008, 40 (3): 263-266

1. NEW CHECKLIST TO HELP MAKE SURGERY SAFER

With major surgery now occurring at a rate of 234 million procedures per year - one for every 25 people - and studies indicating that a significant percentage result in preventable complications and deaths, WHO launched a new safety checklist for surgical teams to use in operating theatres, as part of a major drive to make surgery safer around the world.

“Preventable surgical injuries and deaths are a growing concern,” said Dr Margaret Chan, Director-General of WHO. “Using the checklist is the best way to reduce surgical errors and improve patient safety.”

Several studies have shown that in industrial countries major complications occur in 3% to 16% of inpatient surgical procedures, and permanent disability or death rates are about 0.4% to 0.8%. In developing countries, studies suggest death rates of 5% to 10% during major operations. Mortality from general anaesthesia alone is reported to be as high as one in 150 in parts of sub-Saharan Africa. Infections and other postoperative complications are also a serious concern around the world. These studies suggest that about half of these complications may be preventable.

“Surgical care has been an essential component of health systems worldwide for more than a century,” said Dr Atul Gawande, a surgeon and professor at the Harvard School of Public Health. “Although there have been major improvements over the last few decades, the quality and safety of surgical care has been dismaying variable in every part of the world. The Safe Surgery Saves Lives initiative aims to change this by raising the standards that patients anywhere can expect.”

The Safe Surgery Saves Lives initiative is a collaborative effort led by the Harvard School of Public Health. More than 200 national and international medical societies and ministries of health are working together to reduce avoidable deaths and complications in surgical care. The WHO surgical safety checklist, developed under the leadership of Dr Gawande, identifies a set of surgical safety standards that can be applied in all countries and health settings.

Preliminary results from a thousand patients in eight pilot sites worldwide indicate that the checklist has nearly doubled the likelihood that patients will receive proven standards of surgical care. Use of the checklist in pilot sites has increased the rate of adherence to these standards from 36% to 68% and in some hospitals to almost 100%. This has resulted in substantial reductions in complications and deaths in the 1000 patients. Final results on the impact of the checklist are expected in the next few months.

The checklist identifies three phases of an operation, each corresponding to a specific period in the normal flow of work: before the induction of anaesthesia (“sign in”), before the incision of the skin (“time out”) and before the patient leaves the operating room (“sign out”). In each phase, a checklist coordinator must confirm that the surgery team has completed the listed tasks before it proceeds with the operation.

For example, during the “sign in” phase, the coordinator should check whether the surgical site on the patient’s body was properly marked and whether the patient’s known allergies were checked.
During the “sign out” phase, instruments, sponges and needles should be counted to check that none of these is accidentally left behind in the patient’s body.

The checklist released today will be finalized for dissemination by the end of 2008 once the evaluation of the eight pilot studies is complete.

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2. TWO AND A HALF BILLION LIVE WITH POOR SANITATION FACILITIES

More people using drinking water from safe sources, says a new report

Every day, over 2.5 billion people suffer from a lack of access to improved sanitation and nearly 1.2 billion practise open defecation, the riskiest sanitary practice of all, according to a report issued today by the WHO/UNICEF Joint Monitoring Programme for Water Supply and Sanitation. The programme is the official UN mechanism tasked with monitoring progress towards the Millennium Development Goals (MDG) Target 7c on drinking water supply and sanitation.

The report titled “Progress on drinking water and sanitation - special focus on sanitation,” comes halfway through the International Year of Sanitation. The report assesses -- for the first time -- global, regional and country progress using an innovative “ladder” concept. This shows sanitation practices in greater detail, enabling experts to highlight trends in using improved, shared and unimproved sanitation facilities and the trend in open defecation. “Improved sanitation” refers to any facility that hygienically separates human excreta from the environment.

Similarly, the ‘drinking water ladder’ shows the percentage of the world population that uses water piped into a dwelling, plot or yard, and other improved water sources such as hand pumps, and unimproved sources.

Worldwide, the number of people who lack access to an improved drinking water source (protected from faecal and chemical contamination) has fallen below one billion for the first time since data were first compiled in 1990. At present 87% of the world population has access to improved drinking water sources, with current trends suggesting that more than 90% will do so by 2015.

The number of people practising open defecation dropped from 24% in 1990 to 18% in 2006. The report also highlights disparities within national borders, particularly between rural and urban dwellers.

Worldwide, there are four times as many people in rural areas – approximately 746 million – without improved water sources, compared to some 137 million urban dwellers.

Threats to children’s survival

Poor sanitation threatens children’s survival as a faecally-contaminated environment is directly linked to diarrhoeal disease, one of the biggest killers of infants under the age of five. A clean environment is very difficult to ensure if open defecation is practised even by a minority of the population.

“At current trends, the world will fall short of the Millennium sanitation target by more than 700 million people,” said Ann M. Veneman, UNICEF Executive Director. “Without dramatic improvements, much will be lost.”

However, more and more people are now using improved sanitation facilities, which ensure human excreta are disposed of in a way that prevents them from causing disease by contaminating food and water sources.

Though the practice of open defecation is on the decline worldwide, 18% of the world’s population, totalling 1.2 billion people, still practise it. In southern Asia, some 778 million people still rely on this risky sanitation practice.

“We have today a full menu of low-cost technical options for the provision of sanitation in most settings,” said WHO Director-General Dr Margaret Chan. “More and more governments are determined to improve health by bringing water and sanitation to their poorest populations. If we want to break the stranglehold of poverty, and reap the multiple benefits for health, we must address water and sanitation.”

Real improvements in access to safe drinking water have occurred in many of the countries of southern Africa. According to the report, seven of the 10 countries that have made the most rapid progress and are on track to meet the Millennium Development Goal targets related to drinking water, are in sub-Saharan Africa: Burkina Faso, Djibouti, Ghana, Malawi, Mali, Namibia and Uganda. Of the countries not yet on track to meet the sanitation target, but making rapid progress, five are in sub-Saharan Africa: Benin, Cameroon, Comoros, Mali and Zambia.

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3. NONCOMMUNICABLE DISEASES NOW WORLD’S BIGGEST KILLERS

Chronic conditions like heart disease, stroke kill more, says WHO’s World health statistics 2008

The global burden of disease is shifting from infectious diseases to noncommunicable diseases, with chronic conditions such as heart disease and stroke now being the chief causes of death globally, according to a new WHO report published lately. The shifting health trends indicate that leading infectious diseases – diarrhoea, HIV, tuberculosis, neonatal infections and malaria – will become less important causes of death globally over the next 20 years.

World health statistics 2008 is based on data collected from WHO’s 193 Member States. This annual report is the most authoritative reference for a set of 73 health indicators in countries around the world. These are the best available data and they are essential for painting the global picture of health and how it is changing.

“We are definitely seeing a trend towards fewer people dying of infectious diseases across the world,” said Dr Ties Boerma, Director of the WHO Department of Health Statistics and Informatics. “We tend to associate developing countries with infectious diseases, such as HIV/AIDS, tuberculosis and malaria. But in more and more countries the chief causes of death are noncommunicable diseases, such as heart disease and stroke”.

The statistical report documents in detail the levels of mortality in children and adults, patterns of morbidity and burden of disease, prevalence of risk factors such as smoking and alcohol consumption, use of health care, availability of health care workers, and health care financing. It also draws attention to important issues in global health, including:

- **Maternal mortality:** in developed countries, nine mothers die for every 100 000 live births, while in developing countries the death rate is 450 and in sub-Saharan Africa it is 950.
- **Life expectancy trends in Europe:** life expectancy in eastern Europe increased from an average of 64.2 years in 1950 to 67.8 years in 2005, representing an increase of only about four years compared with 9 to 15 years for the rest of Europe.
- **Health-care costs:** 100 million people are impoverished every year by paying out of pocket for health care.
- **Coverage of key maternal, neonatal and child health interventions:** four out of 10 women and children do not receive basic preventive and curative interventions and at current rates of progress it will take several decades before this gap is closed.

World health statistics 2008 is the official record of data produced by WHO’s technical programmes and regional offices in close consultation with countries and in collaboration with researchers and development agencies. In publishing these statistics, WHO underlines continuing health challenges and provides an evidence base for strategies to improve global public health.


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4. NEW RAPID TESTS FOR DRUG-RESISTANT TB FOR DEVELOPING COUNTRIES

People in low-resource countries who are ill with multidrug-resistant TB (MDR-TB) will get a faster diagnosis -- in two days, not the standard two to three months -- and appropriate treatment thanks to two new initiatives unveiled lately by WHO, the Stop TB Partnership, UNITAID and the Foundation for Innovative New Diagnostics (FIND).

MDR-TB is a form of TB that responds poorly to standard treatment because of resistance to the first-line drugs isoniazid and rifampicin. At present it is estimated that only 2% of MDR-TB cases worldwide are being diagnosed and treated appropriately, mainly because of inadequate laboratory services. The initiatives announced today should increase that proportion at least seven-fold over the next four years, to 15% or more.

“I am delighted that this initiative will improve both the technology needed to diagnose TB quickly, and increase the availability of drugs to treat highly resistant TB,” said British Prime Minister Gordon Brown, who helped launch the Stop TB Partnership’s Global Plan to Stop TB in 2006 and whose government is a founding member of UNITAID. “The UK is committed to stopping TB around the world, from our funding of TB prevention programmes in poor countries, to our support of cutting edge research to develop new drugs.”

In developing countries most TB patients are tested for MDR-TB only after they fail to respond to standard treatments. Even then, it takes two months or more to confirm the diagnosis. Patients have to wait for the test results before they can receive life-saving second-line drugs. During this period, they can spread the multidrug-resistant disease to others. Often the patients die before results are known, especially if they are HIV-infected in addition to having MDR-TB.

The initiative comes just one week after WHO recommended “line probe assays” for rapid MDR-
TB diagnosis worldwide. This policy change was driven by data from recent studies, including a large field trial -- conducted by FIND together with South Africa’s Medical Research Council and National Health Laboratory Services -- which produced evidence for the reliability and feasibility of using line probe assays under routine conditions.

“Five months ago, WHO renewed its call to make MDR-TB an urgent public health priority,” said WHO Director-General Dr Margaret Chan, “and today we have evidence to guide our response. Based on that evidence, we are launching these promising initiatives.”

Two projects

The new initiative consists of two projects. The first, made possible through US$ 26.1 million in funding from UNITAID, will introduce a molecular method to diagnose MDR-TB that until now was used exclusively in research settings. These rapid, new molecular tests, known as line probe assays, produce an answer in less than two days.

Over the next four years -- as lab staff are trained, lab facilities enhanced and new equipment delivered -- 16 countries will begin using rapid methods to diagnose MDR-TB, including the molecular tests. The countries will receive the tests through the Stop TB Partnership’s Global Drug Facility, which provides countries with both drugs and diagnostic supplies.

As part of the project, WHO’s Global Laboratory Initiative and FIND will help countries prepare for installation and use of the new rapid diagnostic tests, ensuring necessary technical standards for biosafety and the capacity to accurately perform DNA-based tests. One country, Lesotho, is already equipped to start using these tests; Ethiopia is expected to be ready by the end of 2008. The tests will be phased in during 2009-2011 in the remaining 14 countries.

Under a second, complementary agreement with UNITAID for US$ 33.7 million, the Global Drug Facility will boost the supply of drugs needed to treat MDR-TB in 54 countries, including those receiving the new diagnostic tests. This project is also expected to achieve price reductions of up to 20% for second-line anti-TB drugs by 2010. All the countries receiving this assistance have met WHO’s technical standards for managing MDR-TB and already have treatment programmes in place. Some will use grants from the Global Fund against AIDS, Tuberculosis and Malaria to purchase the drugs.

“Through the US$ 60-million support provided by UNITAID, these projects are expected to produce significant results in diagnosing and treating patients as well as reducing drug prices and the costs of diagnosis. These efforts illustrate the way in which innovative financing can be deployed for health and development,” said Philippe Douste-Blazy, Chairman of UNITAID’s Executive Board.

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