

KMJ

KUWAIT MEDICAL JOURNAL

The Official Journal of The Kuwait Medical Association

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Editorial

Health Care Reform

Adel K Ayed

Department of Surgery, Faculty of Medicine, Kuwait University, Chest Diseases Hospital, Kuwait

Kuwait Medical Journal 2010; 41 (1): 1-2

The Ministry of Health in Kuwait (MOH), similar to any other health services institution of a government, assumes certain responsibility towards ensuring the wellbeing of its population and is aimed to produce excellent performance results. What triggers their interest in improving the quality of care is the global competition in health care services of modern times and the patients' demand for wider services including medical tourism. The method by which the MOH could achieve measurable improvement is by adopting the process of accreditation and initiating necessary health reforms.

Accreditation is a formal process of evaluation carried out by a recognized body belonging to the government of a country or an independent body constituted towards this end. Through proper scrutinization of the existing health care delivery and a self-assessment followed by peer review against national standards, the MOH could identify the areas requiring improvement. Implementing the recommendations could lead to achieve a higher level of quality and excellence in health care services. Accreditation consists of eight elements that are considered very important to patients as they receive hospital services and these include competence, acceptability, effectiveness, appropriateness, efficiency, accessibility, continuity, and safety. These elements together will provide a comprehensive outlook of the quality of care rendered to the patients.

The goals of accreditation is to ensure patient's safety, maintain and improve the quality of services, promote its effective delivery, create uniformity in health services across the health care system, promote development in health care, and help to achieve public confidence in the entire health care system. The basis for accreditation standards includes first, quality improvement that exists throughout the organization and in all departments and second, patient safety, which involves elimination or minimization of various risks and a careful assessment of adverse events, whenever they occur. The national patient safety

agency in the United Kingdom, 'NHS Direct' describes seven steps to patient safety where NHS is to provide a simple checklist to measure performance in patient safety^[1]. Following these steps will help ensure that the care provided is safe. The seven steps are:

1. Build a safety culture
2. Lead and support your staff
3. Integrate your risk management activity
4. Promote reporting
5. Involve and communicate with patients and the public
6. Learn and share safety lessons
7. Implement solutions to prevent them

Public awareness about the importance of patient safety first cropped up in 1999 with the publication of 'To Err is Human'^[2]. This report estimated that the adverse events arising from health care were the third leading cause of death in the United States^[3]. This finding, along with others, brought patient safety to the top of the policy agenda worldwide.

The International Health Organization is assessing and defining measures to increase performance of their health care system. The key trends that drive changes in the health care industry include: first, rising cost of drugs (6 - 8% per year) and technology (60% per year); second, patients' demand for more closer care like community based setting and chronic diseases management; third, skills shortage which include less nurses and doctors being trained; and fourth, patient safety and quality of care that covers medical errors, and the need for increased disease monitoring due to increasing patient privacy needs.

Health care is expanding and the cost will continue to increase day by day. Significance of the MOH lies in analyzing the relationship between cost expended and the outcome generated. The basic requirement is to determine the quality of the present patient care available to the public compared to that of other countries and to substantiate whether they are

Address for correspondence:

Professor Adel K Ayed, PO Box 24923, Safat 13110, Kuwait University, Faculty of Medicine, Kuwait. E-mail: Adel@hsc.edu.kw

receiving health care based on internationally accepted standards. The evolving issue of medical tourism is one of the challenges encountered by the MOH. People choose to travel for immediate access to doctors and medical services available in one-stop multispecialty centers. Their drive behind such options are multi-factorial, *viz*, lack of perceived quality and service, lack of access to desired kind of treatments, and/or even political situations.

Main objectives of the MOH reform plan is to improve the health financing system, enhance the quality of health care services and broaden the role of the private sector in health service delivery. Like in other countries of the region, Kuwait is facing significant health issues mandating more services due to the increased prevalence of chronic diseases and non-communicable diseases related to life style risks and behavior, such as obesity and diabetes mellitus. Therefore, consideration for public health promotion and disease prevention should be an important step undertaken in health reform.

Multiple studies have shown that coordinated care leads to improved patient safety. The MOH policymakers should consider that team-based approaches to care could result in fewer redundancies and errors. Patients and health care professionals should work together in delivering patient-centered care which includes development of specific treatment plans and determine who will be able to help patients in managing their day-to-day health care. Well-coordinated care is important for patients with chronic diseases, particularly to those patients with multiple health problems. Awareness of technological advances and understanding of recent development in disease biology and genetics are important to health providers. For instance, many patients with certain forms of breast, colon, and prostate cancers could be treated with chemotherapy, radiotherapy and medical intervention. Screening for diseases in certain risk groups is available in the MOH hospitals and patients could be advised on precautions to take before they turn into serious or critical health issues. The emphasis is on improving the safety of patients, treating chronic diseases, and employing new technologies to prevent or cure diseases. Health care providers who want to maintain their practice must expand their knowledge and skills and adopt multidisciplinary approach to care. However, the use of ethical principles and cost-benefit analysis will make appropriate resource allocation decisions and produce consistently excellent health care. Meanwhile, it is important to identify potential leaders in health care who could recognize and contribute to achieve the vision and strategic objectives for the MOH.

Health care reform emphasizes the need for greater primary care and rather fairly distributed use of health care resources by physicians. Health reform goals of decreased cost and improved outcome depend on leadership from the field of academic medicine for advances in clinical research which could contribute to progress human health^[4]. A change in the existing curriculum is needed as well to inspire trainees to pursue clinical research. Clinical discovery research includes application of laboratory science into clinical care as well as clinical epidemiology and health services research. The U.S. Federal government supports expenditure of one billion Dollars to conduct research comparing clinical outcomes, effectiveness, and appropriateness of items, services and procedures that are used to prevent, diagnose or treat diseases, disorders and other health conditions^[5].

It is imperative that health promotion and disease prevention is the primary target to improve health care. We should develop working models and learn from those that work best. Health care must be directed towards enhancing patient contribution towards improving their health along with systems to support this objective. To achieve this, three key elements need to be combined:

1. A strategic approach to provide care with meaningful patient management in addition to identifying various risk factors
2. A delivery system designed to support and coordinate care over time
3. Strategies to pay for prevention and continuity of care. This includes, early intervention and long-term management

Our message that health care reform is a priority for this country and that we would like to participate in the formulation of policy for restructuring the health care system should reach the policy makers.

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Review Article

Therapeutic Approaches to Age-Related Dementias: Rational Search for Effective Drugs

Houda I Nashawi, Mona A Ghazal, Samuel B Kombian
Faculty of Pharmacy, Kuwait University, Kuwait

Kuwait Medical Journal 2010; 42 (1): 3-14

ABSTRACT

Dementia of the Alzheimer's type is a disease associated with age. As the life expectancy of the world population increases, the incidence of dementia is predicted to increase. Currently, very few medications are available that can be used to mitigate the symptoms of the disease. This symptomatic therapy is not optimal and is associated with variable outcomes and side effects. Furthermore, none of these drugs have been clearly proven to stop or prevent the development of the disease. To begin to seriously

address the current poor situation of pharmacotherapeutic management of these devastating diseases, more research is required to understand the pathological changes associated with dementia and to rationally design, synthesize and test compounds with potential for more efficacy and fewer side effects and possibly, disease modifying actions. The ideal compounds would be those which, in addition to providing symptomatic relief, also slow down disease progression with minimal side effects.

KEY WORDS: Alzheimer's disease, conjugated drugs

INTRODUCTION

Dementia is a collective term for a group of neuropsychiatric disorders characterized by cognitive deficit and severe memory impairment. Dementia generally occurs as a result of damage or changes in the brain affecting centers involved in cognition and memory leading to their dysfunction. Dementia can also be caused by infections, head injuries, drugs, or nutritional deficiencies. Dementia often leads to disability. According to the Global Burden of Disease estimates for the 2003 World Health Report, dementia contributed to 11.2% of years lived with disability in people aged 60 years and older, more than stroke, musculoskeletal disorders, cardiovascular diseases, and all forms of cancer^[1]. The patient's ability to function becomes severely impaired and they become totally dependent on their caregiver to perform the simplest day-to-day living tasks. Apart from the devastating psychological and social impact of dementia on patients and their families and caregivers, the economic burden of such diseases is enormous, estimated to be in billions of dollars per year. These include direct costs such as formal medical care and nursing-home care, and indirect costs resulting from the loss of productivity of both the patients and their caregivers^[2].

Many different types of dementias are recognized, including Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, fronto-temporal dementia, hippocampal sclerosis dementia, and others. AD is the most common type of dementia, accounting for about 50% of dementia cases worldwide and afflicting 24-33% of people aged above 85 years in the western world^[3].

AD is a neurodegenerative disorder characterized by mild memory loss that eventually progresses to severe deterioration of intellectual function, personality changes, and speech and language problems. It is a disease in which specific brain regions are targeted early in its course, such as the cholinergic basal forebrain and medial temporal lobe structures including the hippocampus, amygdala, and entorhinal cortex. These areas are responsible for higher learning, memory, reasoning, behavior, and emotional control.

EPIDEMIOLOGY

Nearly 24.3 million people have dementia today and about 4.6 million new cases are diagnosed every year worldwide. The number of people with dementia is estimated to double every 20 years reaching 42 million by 2020 and 81 million by 2040, assuming no changes in mortality, and no effective preventative or

Address correspondence to:

Samuel B Kombian, Faculty of Pharmacy, Kuwait University, P O Box 24923, Safat 13110, Kuwait. E-mail: kombian@HSC.EDU.KW

curative strategies are developed^[4]. This anticipated rise in the prevalence of dementia is attributed to the continuous increase in the average life expectancy of humans as a result of medical advances and improved public health measures and standards of living in many parts of the world, which, although is a positive sign in itself, puts a growing proportion of the population at risk of developing age-related disorders in general, including dementia.

In the Arab World, it is roughly estimated that there are currently more than 1.5 million diagnosed cases of AD^[5]. Unfortunately, accurate, official statistics are lacking. This may be attributed to the lack of specialized institutions (government or private), the educational environment, the administrative systems, and the lack of human and financial resources to keep track of cases of dementia. However, it can be predicted from the available demographic data that the Middle Eastern populations, like in most other countries, are aging too. Life expectancy is increasing as well as the proportion of the population over the age of 60 (Fig. 1)^[6]. Therefore, the prevalence of age-related disorders including AD is expected to rise accordingly, following the general trends in other parts of the world. This highlights the importance of taking quick action to counter the lack of awareness and understanding in the Arab communities of the disease and establishing specialized societies or bodies to offer support for AD patients and their caregivers.

CLINICAL FEATURES

The symptoms of AD can be divided into two main categories: cognitive symptoms and non-cognitive (behavioral and psychiatric) symptoms. The cognitive symptoms are progressive and exist throughout the course of the disease, whereas the behavioral symptoms are variable in their occurrence and are less predictable. There are three clinical stages of AD: mild, moderate and severe. The initial, mild stage usually lasts 2 - 3 years and is characterized by short-term memory impairment often accompanied by symptoms of anxiety and / or depression; this phase is often overlooked and the experienced symptoms are usually attributed to merely "old age". In the moderate stage, neuropsychiatric symptoms appear, such as hallucinations, delusions, and changes in sleep patterns. The severe and final stage is characterized by the appearance of motor signs, such as motor rigidity and prominent cognitive decline. Patients at this stage become unable to communicate and have difficulty understanding others. They also suffer bowel and bladder incontinence and may become confined to bed or a wheelchair. Caregiver burden peaks with the onset of neuropsychiatric symptoms and declines somewhat during the final stage, when the patient is more sedentary^[7]. Life expectancy following disease

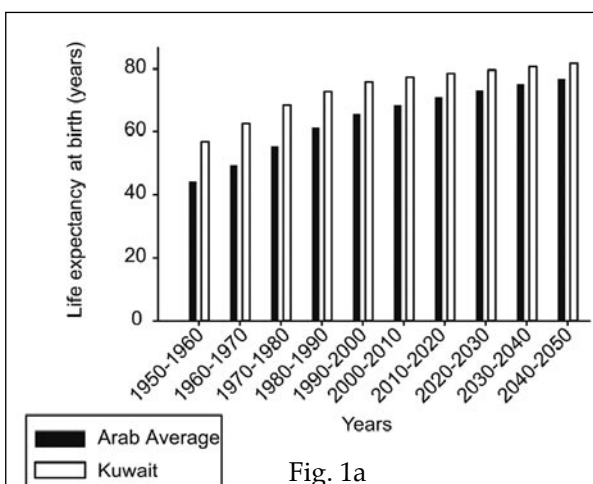


Fig. 1a

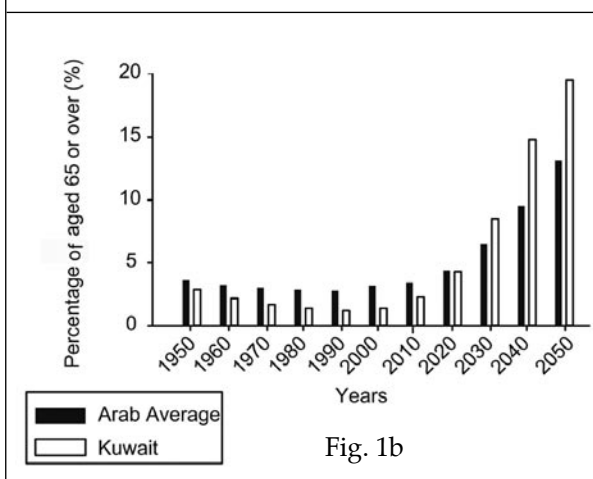


Fig. 1b

Fig. 1: Combined life expectancy of both genders in years (a) and the percentage of population 65-years-old and above (b) in Kuwait and the Arab Region according to the Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. (Statistics from the following countries were used to obtain the average in the Arab Region: Algeria, Bahrain, Comoros, Djibouti, Egypt, Kuwait, Jordan, Lebanon, Libya, Mauritania, Morocco, The Occupied Palestinian Territories, Oman, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, Western Sahara and Yemen).

onset ranges between 3-20 years^[8]. Patients usually die of choking, aspiration, sepsis, malnutrition, or infections, such as pneumonia^[9]. The average survival time is influenced by age at onset and the presence of other medical conditions, such as cardiovascular diseases or diabetes^[10].

Cognitive deficits:

Memory is a broad term representing different areas of cognitive function such as recall, recognition, calculation and orientation. Loss of memory, which means the inability to extract and use all previously learned information, activity, and experience, is the most observable symptom in AD patients. In early AD, the ability to learn and recall recent events is impaired,

while recall for very old events (*e.g.*, memories of childhood or adolescence years) is spared until late stages of AD. Most AD patients forget appointments or lose their personal objects such as keys and they can even get lost in places that were very familiar to them. They can also suffer from disorientation for time, *i.e.*, they may forget the date or day of the week. Later in the course of the disease, patients become unable to perform usual daily activities at home or at work and they may not be able to recall the names of previously familiar people or objects, a phenomenon known as anomia. Other symptoms that can appear in moderate dementia include the inability to perform motor tasks (apraxia), the loss of the ability to draw complex figures or to conceptualize their orientation in space (constructional apraxia) and inability to identify common objects (agnosia). As the disease further progresses, patients experience speech difficulties (aphasia) in addition to extremely impaired judgment, poor decision making, and loss of orientation. They eventually lose the ability to eat, walk, or communicate. They become unable to care for themselves and need continuous supervision and help with all aspects of daily life, which usually results in them being sent to long-term care facilities.

Non-cognitive Symptoms:

The majority of AD patients experience some form or another of non-cognitive symptoms at some point in the course of the disease. Unlike the cognitive deficits that are consistently present in all AD patients, these symptoms vary considerably among patients in their prevalence and severity. The non-cognitive symptoms, also known as the behavioral and psychiatric symptoms (BPS) can be broadly classified into three main groups: depression, psychosis, and behavioral abnormalities^[8]. In early stages of AD, patients may experience changes in personality such as anxiety, irritability, and depression. As the disease progresses, other symptoms such as sleep disorders, agitation (restlessness, irritability, hostility, resistiveness, and pacing), aggression (physical and / or verbal), and psychosis (paranoid delusions and hallucinations) may also occur in median to late stages of AD. The presence of BPS is considered to be one of the main reasons for institutionalization of AD patients by their home-caregivers due to the stress placed on them^[11]. Behavioral symptoms reflect involvement of the frontal and temporal cortices, whereas cognitive symptoms correlate best with the hippocampus and posterior association cortex.

PATHOPHYSIOLOGY

AD is characterized by several structural, microscopic, and neurochemical abnormalities in the brain that distinguishes the disease from other forms

of dementia. It is well established from postmortem examinations of brains of AD patients and from other studies that AD is associated with structural changes in the brain selectively affecting neurons in the hippocampus, basal forebrain, and the neocortex, leading to the shrinkage of these areas known to be critical for learning and memory as well as other higher cognitive functions. It has been shown that in advanced disease, there is diffuse cerebral atrophy with widened sulci and enlarged ventricles.

Microscopically, the two most important pathological hallmarks of AD brains are the presence of senile plaques and neurofibrillary tangles (NFTs). Senile plaques (also known as amyloid plaques or neuritic plaques) are amorphous extracellular lesions found in the brain and cerebral vasculature composed mainly of insoluble aggregates of a 4-kDa polypeptide known as amyloid- β ($A\beta$) protein in addition to other components^[12,13]. $A\beta$ fragments are produced from the proteolytic cleavage of the amyloid precursor protein (APP), which is a trans-membrane protein found in a variety of cells, including central nervous system (CNS) neurons, whose exact function is currently unknown. APP is cleaved by three protease enzymes known as α -, β -, and γ - secretases, which have different sites of action along the APP protein, and the order in which these proteases cleave APP determines whether $A\beta$ is formed. For example, α -secretase cleaves the APP within the $A\beta$ sequence, thus disrupting amyloid formation. On the other hand, cleavage of APP first by β -secretase and then by γ -secretase results in the formation of $A\beta$ which is released into the extracellular space where they aggregate forming senile plaques. Although a correlation between elevated levels of $A\beta$ in the brain and cognitive decline has been demonstrated^[14], it is still unclear how $A\beta$ causes neurodegeneration. It has been suggested that inflammation around the plaques contribute to the destruction of neighboring neurons, and that the presence of such structures in the brain can increase the vulnerability of neurons to ischemia, excitotoxicity, and oxidative stress leading to their destruction.

The other key microscopic finding in AD brains is the presence of NFTs. These are composed of paired helical filaments of a hyperphosphorylated form of the microtubule associated protein, tau^[15]. Tau is a normal axonal protein that binds to microtubules, which are the cell's transportation and skeletal support system, giving them structural stability. Tau's function is regulated by a balance between several kinases and phosphatases. In AD, this balance is disturbed and tau becomes hyperphosphorylated. Hyperphosphorylated tau proteins can no longer bind to microtubules, leading to the disassembly of these microtubules impairing axonal transport and

compromising neuronal and synaptic function^[16]. Hyperphosphorylated tau proteins also become prone to aggregation into insoluble fibrils in tangles, further impairing neuronal function. Whether tau hyperphosphorylation and tangle formation are a cause or consequence of AD is unknown. It is also unclear why tangles are formed, but it has been shown that the density of these filaments within neurons in the brain is highly correlated to the severity of dementia^[17].

The neurochemical abnormalities in AD have been found to involve many neurotransmitter systems, but the most prominent change is a decrease in central acetylcholine (ACh) levels. According to the cholinergic hypothesis in AD, there is a degeneration of cholinergic neurons in the basal forebrain nuclei causing a deficit in cholinergic transmission in the hippocampus and neocortex, which are important for memory and other cognitive and non-cognitive functions^[18]. A progressive loss of nicotinic receptors over the course of AD has also been described, and there is evidence for the involvement of these receptors in memory and cognition deficits^[19]. This hypothesis is supported by many studies reporting a marked decline in cholinergic markers, choline acetyltransferase, and acetyl cholinesterase in the cerebral cortex of the AD brain^[20-22]. These findings led to the presumption that enhancing the cholinergic activity in the brain would improve the symptoms of memory loss, which is the basis of the current mainstay drugs used in the management of AD. In addition, excitotoxicity caused by a sustained low-level stimulation of glutamatergic neurons seems to contribute to the cognitive impairment in AD patients. This stimulation occurs via the chronic influx of Ca²⁺ ions through the N-methyl-D-aspartate (NMDA) receptor channel. Other neurotransmitters, such as dopamine, noradrenaline, and serotonin, can also play a role in cognitive impairment in AD but to a lesser extent.

Like the cognitive symptoms, the etiology of the BPS of AD is not yet completely understood, but it seems that they have both neurochemical and neuropathological correlates that explain their appearance in AD patients. Lower metabolism and perfusion in the frontal and temporal lobes has been observed in AD patients with behavioral disturbances than those patients with fewer behavioral changes. Also, an increased burden of NFTs in the orbitofrontal and anterior cingulate cortex has been associated with patients with persistent agitation^[23]. Changes in the activities of several neurotransmitter systems have also been observed in the brains of patients with BPS. For example, it has been shown that cholinergic deficits contribute to some BPS of AD such as apathy, indifference, aggressive behavior and psychosis^[24].

This has been supported by the observation that patients with BPS have less choline acetyltransferase activity in the frontal and temporal lobes^[23] and that BPS improve in AD patients after administering cholinergic agents such as the acetylcholinesterase inhibitors^[24]. Research has recently shown that alterations in serotonergic activity may also contribute to the overactivity, psychosis, anxiety, agitation, restlessness, and aggressiveness seen in AD patients^[23-25]. It has been suggested that imbalance between the cholinergic and serotonergic systems contributes to the cognitive and BPS of AD^[24]. This hypothesis derives from the finding that selective cholinergic dysfunction together with serotonergic blockade produces severe behavioral deficits while cholinergic dysfunction alone can only produce cognitive and mild behavioral deficits^[24]. It has also been suggested that increased levels of dopamine in discrete regions of the brains of AD patients are responsible for aggressive behavior and psychosis commonly seen in AD patients^[24]. Furthermore, significantly decreased γ -amino butyric acid (GABA) content was detected in the brains of AD patients, which may result in overexcitation leading to the observed symptoms. Recent studies have shown that both GABA levels and the glutamate / GABA ratio significantly correlate with depression in AD^[26]. Finally, reductions in noradrenergic markers have also been reported in AD patients although the exact role of the noradrenergic system in the BPS of AD is not clearly understood.

MANAGEMENT

Treatment of patients with AD should be based on a complete psychiatric, neurological, and general medical examination. It is also equally important to identify and treat other medical conditions patients may have that may contribute to their cognitive and / or non-cognitive symptoms. Since AD is a progressive disorder, the treatment plan must be flexible and evolve with time to address new problems that may emerge as the disease progresses^[27]. Due to the complex nature of AD and its large impact on patients and their caregivers, the management of this complex disorder usually includes both non-pharmacological and pharmacological strategies.

NON-PHARMACOLOGICAL TREATMENT

Similar to any other disease, AD patients and their caregivers must be educated about the nature of the disease, the course of illness, available treatments and their expected effects and side-effects, and prognosis of the disease. In addition to comprehensive counseling and support programs, patients may need psychological therapy that addresses their specific problems, especially their BPS. After ruling out all other conditions that could be contributing

to the patient's symptoms, non-pharmacological interventions are considered to be the first-line approach before attempting to use drugs, and even when pharmacological therapy is initiated, non-pharmacological approaches should be continued as an adjunct that complements pharmacological treatment to help achieve the desired results. A wide range of such interventions are being practiced with AD patients, and increasing number of studies proved their effectiveness for both cognitive and non-cognitive symptoms. Examples include cognitive-behavioral therapy, interpersonal therapy, reality orientation, validation therapy, reminiscence therapy, and supportive psychotherapy^[27-28]. Caregivers of people with AD are also trained in behavioral management techniques, such as problem-solving and memory training, and this has been shown to be helpful in reducing the agitation and anxiety of AD patients in addition to the strain experienced by the caregiver^[29-30].

Providing care for AD patients is often burdensome, not only financially, but also psychologically and physically. It has been found that caregivers themselves are at an increased risk of developing depression, anxiety, and even physical health problems^[31-32]. Factors associated with greater devastating impact on the caregivers include having an affected person at home, the carer being a spouse, and demanding behavior of the patient such as agitation, aggression, hallucinations, sleep problems or walking disruptions, and social isolation^[31,33]. It is therefore encouraged that the caregivers of AD patients who experience psychological distress and negative psychological impact be offered psychological therapies^[34]. Non-pharmacological interventions that specifically target stress and depression among caregivers include cognitive and behavioral family interventions and caregiver counseling support, and these methods have been shown to have positive results on the caregivers and, in turn, on the patients to whom they provide care^[35].

PHARMACOLOGICAL TREATMENT

Treatment of cognitive symptoms: Presently, there is no cure for AD. The only two classes of drugs approved for the management of AD symptoms are anticholinesterases and an NMDA-receptor antagonist. These drugs only produce symptomatic improvement. No drugs to delay or stop the progression of the disease are yet available.

Cholinesterase inhibitors: Based on the cholinergic hypothesis, enhancing cholinergic neurotransmission in the CNS will be expected to improve cognitive symptoms associated with AD. Although this can be done theoretically by several pharmacological means, for example by increasing ACh synthesis,

augmenting its presynaptic release, stimulating postsynaptic nicotinic and muscarinic receptors, or inhibiting ACh degradation by cholinesterases, the only group of drugs that have proven effective so far for symptomatic treatment of AD are the cholinesterase inhibitors. These drugs act by slowing the biochemical destruction of ACh in the synaptic cleft by the hydrolytic enzymes acetylcholinesterase and butyrylcholinesterase, thereby increasing ACh concentration and prolonging cholinergic neurotransmission. The first cholinesterase inhibitor to be approved by the Food and Drug Administration (FDA) of America for the treatment of AD was tacrine, which was introduced in 1993. Although this drug was shown to be effective in clinical trials^[36], it has fallen out of use because of its inconvenient dosing regimen (it had to be given four times daily due to its short half-life) and hepatotoxicity associated with its use. The currently used, "second generation" cholinesterase inhibitors are donepezil, rivastigmine, and galantamine. The three drugs have been shown to be efficacious and relatively safe in humans and are currently being used for the symptomatic treatment of mild to moderate AD. These drugs share a similar mechanism of action but differ in their pharmacokinetics and their selectivity for the two cholinesterases in the human brain. Their efficacy has been studied in several randomized, double-blind clinical trials and all have shown modest positive effects on cognitive symptoms with similar efficacy among them. These drugs have also been shown to have some benefit for BPS of AD. However, they are not expected to alter the natural course of AD but only to temporarily alleviate its symptoms. Their side-effects are mainly gastrointestinal including nausea, vomiting, diarrhea, and anorexia, which can be intolerable especially in low-weight patients. Other side-effects include bradycardia, syncope, and muscle cramps that occur due to excessive cholinergic stimulation.

NMDA receptor antagonists: A more recently approved drug for use in the treatment of AD is memantine, an NMDA receptor antagonist. The rationale for the development and use of this drug is based on the observation that glutamate-mediated excitotoxicity that results from excessive activation of NMDA receptors may have a role in neuronal damage in AD. It is believed that this glutamatergic overstimulation leads to increased intracellular Ca²⁺ which then triggers downstream events that can lead to neurodegeneration. Accordingly, it is believed that non-competitive NMDA receptor antagonists, with fast blocking / unblocking kinetics like memantine, would be able to protect neurons from the effect of abnormal, excessive glutamatergic activation while

Table 1: Dosage regimen of currently used cholinesterase inhibitors and memantine

	Donepezil	Rivastigmine	Galantamine	Memantine
Therapeutic category	Acetylcholinesterase inhibitor	Acetylcholinesterase inhibitor	Acetylcholinesterase inhibitor	NMDA receptor antagonist
Indication	Mild to moderate AD	Mild to moderate AD	Mild to moderate AD	Moderate to severe AD
Initial dose	5 mg/day	1.5 mg twice daily	4 mg twice daily	5 mg / day
Dose titration	Every 4-6 weeks.	Every 2 weeks, until recommended or tolerated dose reached.	Every 4 weeks, until recommended or tolerated dose reached.	Every week until recommended or tolerated dose reached.
Recommended target dose	10 mg/day	3-6 mg twice daily	8-12 mg twice daily	10 mg twice daily

preserving the physiologic activation of NMDA receptors required for learning and memory. Clinical trials show modest positive effects of memantine on cognitive and behavioral symptoms in moderate to severe cases of AD and it is reported that the drug is generally well-tolerated with fewer side-effects than those of cholinesterase inhibitors. The dosage regimens followed with the four currently used drugs are listed in Table 1, and their common side effects are listed in Table 2.

Nootropic agents: Nootropic agents (or cognitive enhancers) are drugs that enhance memory and learning, motivation, attention and concentration without having the sedative or stimulating effects of other psychoactive agents. The prototype nootropic agent is piracetam, which is marketed for the treatment of a wide range of organic psychosyndromes, cerebrovascular accidents, and as an adjunctive treatment of cortical myoclonus^[37]. It has also been used to treat children with dyslexia and patients with AD, among other

cognitive disorders. At doses reported in the literature for these indications, piracetam appears to be relatively non-toxic, and serious adverse reactions associated with its use have not been commonly reported.

In many studies, piracetam significantly improved learning, the performance of perceptual-motor tasks, and mental alertness^[38-40]. It has also been shown to cause neuronal regeneration and to increase neuronal receptor density^[40-41]. However, the precise mechanism of action of nootropics is not yet completely well-known. They have been found to enhance dopamine release, a neurotransmitter believed to have a role in information acquisition^[42-43], which may explain some of the beneficial effects of nootropics on memory formation. Piracetam also improves cholinergic activity via muscarinic ACh receptors as well as glutamatergic activity on glutamate NMDA receptors, both of which are implicated in memory processes^[44]. Other racetams include oxiracetam, pramiracetam, aniracetam,

Table 2: Common adverse effects of cholinesterase inhibitors and memantine from clinical trials data (Modified from^[8])

Adverse effect	Tacrine (%)	Donepezil (%)	Rivastigmine (%)	Galantamine (%)	Memantine (%)
CNS					
Headache	11	10	17	8	6
Dizziness	12	8	21	9	7
Insomnia	6	9	9	5	-
Depression	4	3	6	7	-
Somnolence	4	2	5	4	3
Agitation	7	-	-	-	-
Gastrointestinal					
Nausea or vomiting	28	-	-	-	-
Nausea	-	11	47	24	-
Vomiting	-	5	31	13	3
Diarrhea	16	10	19	9	-
Abdominal pain	8	-	18	5	-
Anorexia	9	4	17	9	-
Elevated liver enzymes	29	-	-	-	-
Neuromuscular					
Tremor	2	-	4	3	-
Muscle cramps	9	6	-	-	-
Respiratory					
Rhinitis	8	-	-	-	-

and levetiracetam, the latter being marketed as an anticonvulsant agent for the treatment of epilepsy.

TREATMENT OF NON-COGNITIVE SYMPTOMS

Since the BPS symptoms of AD are usually the most distressing, it is important that these symptoms are treated as well. Good practice is to first rule out any physical causes of the BPS (*e.g.*, infection, pain, other disease conditions or medications) and to start with non-pharmacological strategies to manage the symptoms. Should these approaches fail to control the symptoms, pharmacological therapies may then be initiated. The choice of drugs should be based on agent-related factors (*e.g.*, side-effect profile, interactions, cost) and patient-related factors (*e.g.*, disease states or administration needs). Care should be taken when prescribing medications for AD patients not to use drugs that can exacerbate their symptoms.

Antipsychotics are widely used to treat disruptive behavior and psychosis in AD patients. BPS that have been shown to respond to antipsychotic use include agitation, hyperexcitability, hallucinations, delusions, hostility, and uncooperativeness^[45-46]. Earlier, typical antipsychotics, such as haloperidol, were used. However, these agents are no longer recommended for use in elderly patients because of the associated high incidence of extrapyramidal and anticholinergic side-effects, to which AD patients generally seem to be more sensitive. The current treatment of choice for psychosis and aggression in AD patients are the atypical antipsychotics, of which risperidone, olanzapine, and quetiapine have data supporting their use in such cases^[8,47].

Antidepressants can be prescribed to treat AD-associated depression. Tricyclic antidepressants (TCAs) are not suitable for AD patients also because of their anticholinergic side-effects, which are especially prominent with agents like imipramine and amitriptyline. Selective serotonin reuptake inhibitors (SSRIs), such as citalopram, fluoxetine, and paroxetine, are the preferred treatment for depression in demented patients. The use of serotonin/norepinephrine reuptake inhibitors (SNRIs; *e.g.*, venlafaxine), mirtazapine, and bupropion is also acceptable^[27,47].

Sleep disturbances can be treated with sedating antidepressants (*e.g.*, trazodone, mirtazapine) or non-benzodiazepine sedatives (*e.g.*, zolpidem, zaleplon)^[27,47]. Benzodiazepines should be avoided because of risks of lingering daytime sedation, tolerance, rebound insomnia, impaired cognition, disinhibition (which worsens agitation and aggression), and falling in elderly patients^[27,48-49]. Diphenhydramine is not recommended as well due to its anticholinergic properties^[27]. In all cases, maintaining daytime activities and good sleep

hygiene should be ensured, which also can help overcome sleep problems in AD patients.

In addition, many studies concluded that cholinesterase inhibitors have modest beneficial effects in treating neuropsychiatric symptoms and reducing functional impairment in patients with mild to moderate AD^[24,50].

FUTURE DIRECTIONS

The fact that none of the available medications are curative or are able to substantially alter the progress of AD (but see Cosman *et al.*, 2007^[51] on memantine) necessitates the search for new drugs for this disease. This is especially important as the prevalence of AD and consequently its personal, psychosocial, and financial burdens are continuously increasing. Unless major efforts are made to develop drugs that are more effective, more tolerable, or that can stop or at least significantly decelerate the progression of this disabling disease, the burden on the society will continue to rise. Advances in the knowledge of the pathogenesis of AD can help in identifying potential drug targets and in developing new therapeutic strategies that can have disease modifying effects rather than merely addressing the symptoms. Also, continued epidemiological studies may provide some insight into factors that are associated with a lower risk of the disease, which can be exploited as part of future management or strategy for treatment. More than 600 clinical trials are investigating possible treatments for AD^[52]. Unfortunately, in the past two years since these authors started reviewing the literature in this area, no new agents have entered the market^[53]. Potential strategies include secretase modulators, amyloid immunotherapy, anti-tau therapies, treatment approaches based on epidemiological data and conjugated agents (*e.g.*, xanthine and racetam derivatives).

Secretase modulators

Since A β protein is the major component of senile plaques and these plaques correlate with cognitive decline in AD patients, it is possible therefore that inhibiting A β production (and consequently plaque formation) by modulating the action of the enzymes involved in APP processing is likely to prevent or at least delay the onset of AD or slow its progression. α -, β -, and γ -secretases are the three enzymes involved in APP processing, and compounds that can modulate their action are being studied as potential anti-AD drugs.

As mentioned earlier, APP processing by α -secretase does not result in toxic A β formation, suggesting that promoting APP metabolism through this pathway can be neuroprotective. In addition, some research has found that some products of APP

processing by α -secretase can have neuroprotective effects as well^[54-55]. Research is being done to find ways to enhance the action of α -secretase, and it has been shown so far that this can be achieved by using protein kinase C (PKC) isoenzymes that stimulate α -secretase activity^[56] or by PKC activators such as bryostatin, an investigational anticancer agent that has been found to enhance α -secretase function and reduce A β generation in AD transgenic mice^[57]. It has also been found that some ACh muscarinic M1 and M3 receptor agonists enhance α -secretase function and decrease A β production through activating PKC^[58-59].

Another way to prevent A β formation is to inhibit the enzymes β - and γ -secretases. In β -secretase knockout mice, A β production was reduced to minimum and these mice were shown to be healthy and free of any serious abnormalities that might have resulted from β -secretase absence^[60-62]. This suggests that β -secretase inhibition can be a promising therapeutic approach for AD management that can reduce A β production with potentially no major side effects. However, the development of such inhibitors is presently quite challenging. This is because while the ideal inhibitor should be of small size and sufficiently lipophilic to cross the blood-brain barrier and achieve high brain concentrations, the X-ray structure of β -secretase has revealed a large active site, which might not be sufficiently blocked by such small molecules^[63]. Several β -secretase inhibitors, nevertheless, have been developed, and they have been shown to reduce A β concentrations in the brains of AD transgenic mice^[64]. So far, none of these agents have advanced to clinical trials.

As for γ -secretase, many pharmaceutical companies are currently competing to come up with an inhibitor of this enzyme that is effective in reducing A β with minimal side-effects. However, unlike the case with β -secretase, knockout of the presenilin 1 gene that encodes a protein essential for γ -secretase function caused a lethal phenotype, which indicates that γ -secretase may be involved in vital signaling pathways and has protein substrates other than APP, such that interfering with these pathways becomes lethal. "Notch", for example, is a protein involved in signaling pathways crucial for normal embryonic development and for the differentiation of mitotic cells in the bone marrow later in life. This protein requires the action of γ -secretase to be functional^[65]. Nevertheless, some γ -secretase inhibitors have been developed that do not affect "notch" signaling^[66] and several have shown good tolerability in clinical studies. For example, in 2001, Bristol-Myers Squibb announced that the first γ -secretase inhibitor had entered phase

II clinical trials but no results of these trials have yet been published. Another compound, LY-450139 (by Eli Lilly), has been given to AD patients for six weeks in a phase II clinical trial and was found to significantly reduce plasma A β concentrations at a dose that did not produce significant side effects, although only a small, insignificant decrease in A β in the CSF was detected^[67]. As well, the compound MK-07521 (by Merck) was also studied in phase I clinical trials where it was reported to reduce A β levels in the CSF with no serious side effects^[68]. Tarenflurbil (MPC-7869; Myriad Pharmaceuticals) is a drug belonging to a group of compounds known as selective amyloid lowering agents (SALAs). The SALAs are found to inhibit A β formation without interfering with other γ -secretase substrates. In a 12-month, phase II, randomized clinical trial including 207 patients, tarenflurbil was shown to improve cognition and function in patients with mild, but not moderate AD^[69]. Tarenflurbil is currently being studied in phase III trials in patients with mild AD.

A β immunotherapy

An alternative approach to reduce A β in the brain would be immunization against A β protein. It has been shown that active immunization with A β reduces A β deposition^[70] and improves learning and memory deficits in AD transgenic mice^[71-72]. Similar results were obtained using passive immunotherapy with antibodies against A β ^[73]. It has been postulated that these effects may be mediated by anti-A β antibodies that bind to A β plaques and induce A β clearance by microglia, or by binding soluble A β in the periphery, thereby driving an A β efflux from the brain^[73]. The results from animal studies were encouraging enough to study this approach in human subjects. However, the first clinical trial of active A β immunization using the vaccine AN-1792 (aggregated A β 42) was terminated because of the development of meningoencephalitis in 6% of the treated subjects^[74]. The reaction was thought to be a result of T-cell activation against the mid-terminal and C-terminal parts of the peptide. Therefore, the second generation of active vaccines composed of A β conjugated to a carrier protein to allow for active immunization with reduced side-effects^[75]. This approach is currently being studied in phase II clinical trials with the immunoconjugate ACC-001^[75]. Finally, the safety and tolerability of the A β monoclonal antibody bapineuzumab (AAB-001) has advanced to phase III clinical trials for passive immunization^[76].

Anti-tau therapies

NFT load has been found to correlate with cognitive impairment and the formation of these tangles has been proposed to be the result of hyperphosphorylation

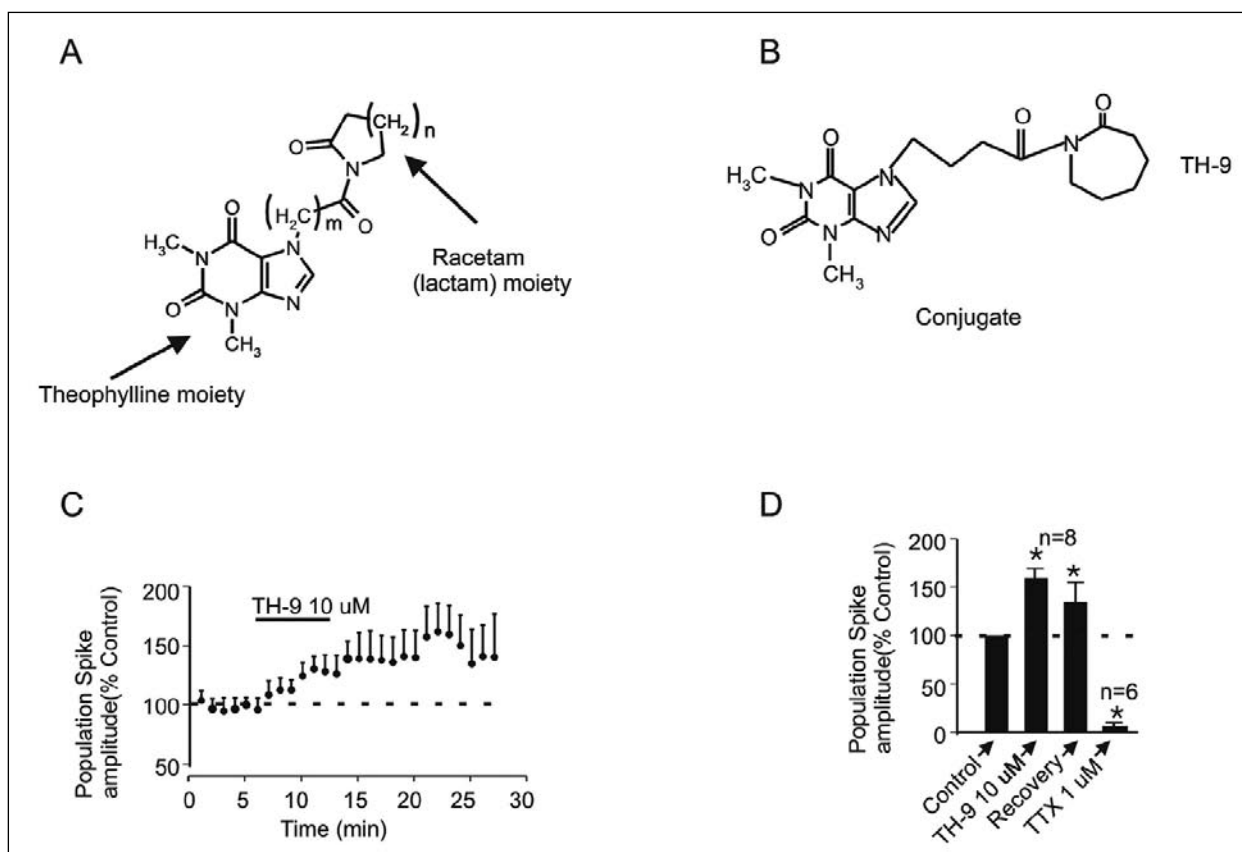


Fig. 2: Conjugated methylxanthine and lactam compounds and their action on hippocampal neuronal communication. (A) Generic structure of conjugates and (B) complete structure of prototype active compound which enhances neuronal communication (C & D) recorded *in vitro* in the rat hippocampal slice preparation. (Adapted from [80])

of tau proteins due to an imbalance between kinase and phosphatase activity. Therefore, inhibiting tau kinases or stimulating tau phosphatases should, in theory, restore the balance and could have therapeutic benefits. Despite this, tau as a therapeutic target has not received as much attention from the pharmaceutical industry as A β , perhaps because well-characterized mouse models of tangle formation have only recently become available^[77]. Targets that are now being investigated in preclinical studies include cyclin-dependent kinases (CDKS) and glucogen synthase kinase (GSK)-3- β , both of which are enzymes believed to be involved in tau hyperphosphorylation and NFT formation.

Therapeutic approaches based on epidemiological studies

Numerous epidemiological and observational studies have shown that the use of non-steroidal anti-inflammatory drugs (NSAIDs), HMG-CoA reductase inhibitors (statins), anti-oxidants (such as vitamins C and E), and hormone replacement therapies (in postmenopausal women) is associated with a lower risk for developing AD. These agents are being intensely studied in both animal models and clinical trials in order to verify the epidemiological

observations, to find their possible mechanisms of action in AD, and to identify potential preventative or therapeutic targets for the development of new drugs to manage AD.

Conjugated drugs

Methylxanthine, or xanthines (3,7-dihydropurine-2,6-diones) in general, are purine-base alkaloids found in many plants. Most common sources are coffee, tea, cocoa, and cola nuts (used in soft drinks). Foods and beverages containing these compounds are long believed to elevate mood, decrease fatigue, facilitate wakefulness, and improve mental concentration and capacity for work, which is why they are very popular and a significant part of many cultural practices and diets. Pharmacological studies confirmed some of these beliefs and have revealed that the main compounds responsible for these effects are caffeine, theophylline, and theobromine. Numerous studies on both animals and humans have shown that these compounds do have significant effects on motor activity, learning and memory, simple and complex coordination, behavior and mood, anxiety and sleep^[78-79]. Based on these findings, a series of compounds combining the methylxanthine structure and the racetam *via*

the lactam ring (the primary structure of the racetam nootropics such as piracetam) were synthesized and studied to see if these compounds would have nootropic effects^[80]. Initial *in vitro* studies revealed that some of these compounds generally enhance synaptic transmission and neuronal activity in the hippocampus through a mechanism distinct from that reported for the primary methylxanthine structure (Fig. 2)^[80]. Furthermore, preliminary studies in our laboratory suggest that these "nootropic" conjugates also enhance long-term potentiation (LTP), a cellular model for learning and memory, in rat hippocampal slices *in vitro*. These findings suggest that these compounds may be of benefit as memory enhancers in AD patients. Studies are ongoing to further explore whether these actions are superior to existing nootropic agents and whether they would demonstrate *in vivo* nootropic actions in animals.

CONCLUSION

Research is increasingly focusing on developing novel drugs for AD that can do more than temporarily alleviating the symptoms of this disabling, age-related neurologic disease. The importance for the development of new efficacious and safe drugs arises from the fact that human life expectancy and the proportion of the elderly in the general population is continuously rising. Besides the currently available cholinesterase inhibitors and the glutamate antagonist memantine, potential new therapies for AD that are under investigation include secretase modulators, A β vaccines, anti-tau therapies, and conjugated compounds in which the chemical structures of available nootropic agents are chemically combined to come up with new ones that could be more effective. In addition, NSAIDs, antioxidants, statins and hormones have been found to be associated with lower risk of AD, and are consequently being studied as potential therapies. The hope is that some of these new treatment approaches and / or drugs would help prevent the disease and / or slow its progression. Arab countries, like the west, are benefiting from improved health care and nutrition accompanied by a gradual shift in the demographics towards later years and hence the need to take action to establish specialized national or regional organizations that care for AD patients and promote community awareness of this increasingly prevalent disease.

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Original Article

Relationship between Ongoing Learning Approaches and Development of Clinical Reasoning Ability

Cihat Tetik¹, Peter Harris², Philip Crowe³¹Department of General Surgery, School of Medicine, Pamukkale University, Denizli, Turkey²Department of Public Health and Community Medicine, Faculty of Medicine, The University of New South Wales, Sydney, Australia³Department of Surgery, Faculty of Medicine, The University of New South Wales, Sydney, Australia

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ABSTRACT

Objective: There are close similarities between the advice for improving clinical reasoning and characteristics of students with a deep learning approach. No study in the literature has explored the relationship between ongoing learning approaches and clinical reasoning ability. This study was designed to explore this relationship.

Design: Cross sectional study

Setting: A single medical school at the University of New South Wales

Subjects: Two hundred and sixty year-4 students were invited to participate voluntarily in this study after institutional ethics approval was obtained

Interventions: The Revised Two-Factor Study Process Questionnaire and Diagnostic Thinking Inventory (DTI)

were used. A potential relationship between these two variables was explored using the Pearson correlation.

Main Outcome Measures: Learning approaches and clinical reasoning abilities of participants

Results: One hundred and eighty two out of 216 (84.3%) students responded. There was a significant positive correlation between deep approach and DTI scores while there was a significant negative correlation between surface approach and DTI scores.

Conclusions: Ongoing deep approach of early clinical students can improve the development of their clinical reasoning ability while ongoing surface approach may impair this ability. Evaluating ongoing learning approach may be important in sustaining clinical reasoning development.

KEY WORDS: cognition, study characteristics, undergraduate

INTRODUCTION

Students in medicine are expected to acquire and develop clinical reasoning ability during their clinical education. Clinical reasoning has been described as the thinking and decision making processes associated with clinical practice. As one of the core elements of clinical reasoning, cognition, described as the thinking process is related to the knowledge structure in the student's memory^[1]. This knowledge structure and the ways of thinking are formed by the learning process that the student follows. Accordingly, the development of clinical reasoning ability should be associated with the students' learning approach during the process of study, *i.e.*, their ongoing learning approach. The approach to learning has been widely studied using the Study Process Questionnaire (SPQ) and more recently the Revised Two-Factor Study Process Questionnaire (R-SPQ-2F)^[2]. Deep learners are described as

employing strategies that enable them to make their own meaning of the topic under study. There appear to be close similarities between the advice for improving clinical reasoning and characteristics of students with deep learning approach.

Sobral claimed that better clinical reasoning ability is associated with high motivation to learn and with an abstract learning type^[3]. In that study, students' learning characteristics were assessed at the beginning of, rather than during the study process. McManus *et al* found no significant correlation between preferred learning approaches at the beginning of the course and the final examination but did find some correlation between learning approaches late in the course and the final examination^[4]. This current study was planned to explore, if a relationship exists between students' ongoing learning approaches and their development of clinical reasoning ability.

Address correspondence to:

Dr. Cihat Tetik, Associate Professor, Department of General Surgery, School of Medicine, Pamukkale University, Denizli, 20070, Turkey.
Tel: +90 - 506 511 1811, Fax: +90 - 258 296 2433. E-mail: ctetik@pamukkale.edu.tr

SUBJECTS AND METHODS

The subjects were students at a single medical school with a six-year high school entry undergraduate medical program. Year 4 students were invited to participate voluntarily after institutional ethics approval was obtained.

Two different measurement tools were used. To describe students' approaches to learning the R-SPQ-2F^[2] was selected. Ten out of 20 items in this questionnaire relate to a deep approach and the others to a surface approach. The maximum possible score is 50 for each of deep or surface approaches whereas the minimum possible score is ten for each approach. For this study, students with deep approach scores greater than surface approach scores were grouped as deep learners, whereas students with greater surface approach scores were surface learners^[2]. Those students who scored equally on deep and surface approach scores were referred to as neutral learners in this study.

The tool selected to assess participants' clinical reasoning ability was the Diagnostic Thinking Inventory (DTI). Clinical reasoning is complex and varies according to the expertise of the practitioner. To investigate this phenomenon, Bordage developed the DTI that is reported to be independent of a student's level of medical knowledge^[1]. The DTI is reported to be a reliable tool to assess clinical reasoning ability^[1] independent of clinical knowledge and has been used by different researchers^[3, 5-8]. The DTI has 21 items exploring flexibility in thinking and the remaining 20 exploring knowledge structure in memory. Both scores are added to calculate the score of diagnostic thinking ability. Both tools, R-SPQ-2F and DTI, were administered concurrently.

Pearson correlation coefficient was used to examine a potential relationship between two variables.

RESULTS

One hundred and eighty-two out of 216 (84.3%) students filled out the questionnaires.

One hundred and twelve of the 182 (61.5%) students were deep learners, 63 of them (34.6%) were surface learners and the remaining seven (3.8%) students were neutral learners.

The students had a mean DTI of 162.71, with deep learners having a mean of 169.25 (15.89) and surface learners, a mean of 153 (12.88). The difference between the mean values of both groups' DTI scores was statistically significant ($p < 0.001$, 95% confidence interval).

There was a significant correlation between deep learning approach and DTI score using the Pearson correlation ($p < 0.01$, 95% confidence interval). On

Table 1: Correlation between the scores of R-SPQ-2F and DTI

Score category	Knowledge structure in memory	Flexibility in thinking	DTI score
Deep motivation score	0.45 *	0.27 *	0.41 *
Deep strategy score	0.48 *	0.26 *	0.41 *
Deep approach score	0.50 *	0.29 *	0.44 *
Surface motivation score	-0.39 *	-0.32 *	-0.40 *
Surface strategy score	-0.46 *	-0.34 *	-0.45 *
Surface approach score	-0.46 *	-0.36 *	-0.45 *

* $p < 0.01$. Correlation is significant at the 0.01 level (2-tailed)

the other hand, there was a significant negative correlation between a surface learning approach and DTI score ($p < 0.01$, 95% confidence interval) (Table 1).

DISCUSSION

The learning characteristics of the deep learners parallel most of the elements in the advice offered to students to help them develop clinical reasoning ability^[9] and those characteristics of adult learners^[10] which facilitate the development of clinical reasoning ability. Students adopting deep approach are interested in the reality and like to know the relationship between the topic and real-life problems. They are expected to watch carefully for whatever is important during the clinical reasoning process at the bed-side or when checking and discussing patients' files. Thus, it would be expected that students who adopt a deep approach should develop clinical reasoning ability more readily than surface learners. As expected, mean values of DTI scores of the deep learners in this study are higher than those of surface learners.

According to Biggs' 3P (Presage, Process and Product) Model of Study Processes, students' preferred approaches to learning affect learning-focused activities and learning outcomes^[2,11,12]. At the beginning of a study process, students approach their learning activities using these preferred learning methods. During their study process, students are affected by teaching context related factors such as learning objectives, teaching environment and style, assessment methods and feedback about their progress and accordingly, they can change their learning approaches slightly or significantly^[2,11,12]. As a result, the preferred learning approach of a student at the beginning may be different from their ongoing learning approach during their study process. Both preferred and ongoing learning approaches affect learning outcomes^[2]. One of the learning outcomes of medical education is the development of clinical reasoning ability. Thus, it can be expected

that the development of clinical reasoning ability is influenced by an individual's preferred and ongoing approaches to learning.

The knowledge gathered before the clinical attachment affects the development of clinical reasoning ability because medical knowledge is one of the core elements of clinical reasoning. Knowledge related to the clinical reasoning process is organized during the study process and students develop thinking ways for using this knowledge by observing the experts and practicing their own clinical reasoning^[13-15]. Organization of knowledge and utilization of thinking ways have been reported as the determinants of cognitive abilities during the clinical reasoning process^[13, 16-18]. Thus, the development of clinical reasoning ability is influenced by learning activities such as observation of the experts and clinical reasoning practice during the process of study. These learning-focused activities are influenced by ongoing learning approaches^[2].

One of the characteristics of students with a deep approach is a searching ability for the integration of knowledge across different subjects and relating new ideas with previous knowledge^[19]. This is quite different from the memorization process of students with a surface approach. These students would try to memorize others' clinical reasoning skills observed in similar clinical situations. This learning strategy does not help to develop clinical reasoning ability because memorization process without integration of knowledge impairs organization of knowledge structure. Thus, in order to assess the relationship between learning approaches and the development of clinical reasoning ability, the measurement of ongoing learning approaches would be important. The current study revealed a relationship between ongoing learning approaches and clinical reasoning ability. This is the first study reporting this relationship. Previous studies^[3,4] did not explore relationship between students' learning approaches during the study process and clinical reasoning ability. As a major limitation, this study was carried out in one school only. A general study including many universities would give crucial data supporting the claims in this study.

CONCLUSIONS

The current study presents evidence that the ongoing deep approach to learning is associated with the development of clinical reasoning ability positively while the ongoing surface approach is associated negatively. Ongoing learning approaches of students assessed by R-SPQ-2F are statistically correlated with the participants' clinical reasoning ability evaluated by DTI. We conclude that ongoing

deep approach of early clinical students can improve the development of their clinical reasoning ability while ongoing surface approach may impair this ability. Evaluating ongoing learning approach may be important in sustaining clinical reasoning development.

These findings apply to students beginning their clinical reasoning. Each student was a novice in this skill. This study is intended to assist those involved in introducing clinical reasoning to their students and does not address the performance or development of advanced clinicians. The question now to be asked is what would happen to the development of clinical reasoning skills if the ongoing learning approaches of early clinical students change.

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Original Article

Clinical and Biochemical Characteristics of Early Onset Type 2 Diabetes in Kuwaiti Youth

Soliman A El Gebely, Waleed A Aldahi, Medhat M S Abdel-Shahid
Department of Medicine, Mubarak Hospital, Kuwait

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ABSTRACT

Objectives: To assess clinical features and investigation results in early onset type 2 Kuwaiti diabetics

Design: Descriptive study

Setting: Mubarak Alkabeer Hospital, Kuwait

Subjects: Nineteen early onset type 2 diabetics

Main Outcome Measures: Clinical features and investigation results

Results: All patients were overweight ($n = 6, 16\%$) to obese ($n = 13, 84\%$) at diagnosis with a mean BMI of 31.43 ± 2.09 kg/ m² and a mean waist circumference of 94 ± 1.7 cm in females and 103.43 ± 1.24 cm in males. Hypertension was reported in three cases with mean systolic blood pressure of 134.32 ± 8.45 and mean diastolic blood pressure (DBP) of 87.05 ± 10.34 . Family history of type 2 diabetes was reported in 68.4% and maternal history of gestational diabetes in 52.6%. Ten patients (52.6%) had *acanthosis nigricans*. Six

female patients (out of 12) had clinical features of polycystic ovary syndrome. Homeostasis model assessment was found to have strong positive correlation with BMI, waist circumference in females, triglycerides (TG) and DBP; and negative correlation with high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1. Similarly, high-sensitive C-reactive protein showed positive correlation with BMI, waist circumference in female and male patients, TG and DBP; and negative correlation with HDL-C.

Conclusion: Early onset type 2 DM is increasingly recognized in Kuwait. This phenomenon is strongly associated with obesity; in particular central adiposity and chronic inflammatory states which appear early in these youngsters. Type 2 DM is frequently asymptomatic and should be considered in obese adolescents with positive family history.

KEY WORDS: high sensitive CRP, insulin resistance

INTRODUCTION

As in adults, type 2 diabetes (DM) in the young is emerging as an increasingly prevalent disorder^[1,2]. Genetic and familial factors^[3], fetal environmental factors, particularly maternal gestational diabetes and intrauterine growth retardation^[4], lifestyle factors especially lack of physical activity during childhood and adolescence lead to increasing levels of insulin resistance that appear to be crucial in the pathogenesis of type 2 diabetes in the young^[5].

It is suggested that, the diabetogenic process in early onset type 2 diabetes begins as early as in fetal life, with low birth weight and poor nutrition combined with later sedentary lifestyle and dietary factors which lead to insulin resistance with increased prevalence of obesity and type 2 DM^[6].

The diagnostic criterion for diabetes is fasting plasma glucose greater than 7.0 mmol/l or 2-h post-prandial glucose greater than 11.1 mmol/l on an oral glucose tolerance test. A raised C peptide or insulin level and negative autoantibodies to islet cell (ICA)

or glutamic acid decarboxylase (GAD), together with obesity, positive family history and signs of insulin resistance can help to distinguish between both type 1 and type 2 diabetes^[7]. Early onset type 2 diabetes is distinct from maturity-onset diabetes of the young (MODY) which is a rare form of diabetes associated with genetic defects in beta-cell function inherited in an autosomal dominant fashion. Although MODY is clinically and genetically heterogeneous, the underlying defects do not produce insulin resistance^[8].

Type 2 DM in the young, is an important precursor to future morbidity from cardiovascular or renal disease and has become a clinical and health economic priority, with important implications as a health care burden throughout the world. Follow-up data are scarce but serious complications of diabetes are known to occur within 10 years of diagnosis and in the early 3rd decade of life^[9,10].

The aim of this study is to describe the demographic, clinical and biochemical characteristics of early onset type 2 DM in a series of young Kuwaiti diabetics.

Address correspondence to:

Dr Soliman A El Gebely, Dept. of Medicine, Mubarak Alkabeer Hospital, Jabriya, Kuwait. E-mail: solimanfarah@yahoo.com; mabdel_shahid@yahoo.com

SUBJECTS AND METHODS

This is a descriptive study of a series of young Kuwaiti diabetic patients who presented with early onset type 2 diabetes to our diabetes unit at the Mubarak teaching hospital (university affiliated), Faculty of Medicine, Kuwait. Nineteen young type 2 diabetic patients were selected from a total of 197 recently diagnosed type 2 diabetics who presented to the hospital during 2005 - 2006 based on the following inclusion criteria:

1) Age: 15 – 20 years, 2) A positive family history for type 2 diabetes in a parent, and 3) Evidence of insulin resistance : obesity: BMI > 30 kg/m²; central adiposity: WC (female > 88 cm, male > 102 cm); presence of *acanthosis nigricans*; features of polycystic ovarian syndrome (hirsutism, irregular menses and hyperandrogenemia) among females; biochemical evidence of raised C peptide, serum insulin and insulin resistance calculated by homeostasis model assessment (HOMA).

Exclusion criteria

1) DM with positive autoantibodies, 2) Maturity-onset diabetes of the young (MODY), non-obese with predominant horizontal family history, and no evidence of insulin resistance clinically and biochemically, and 3) Cardiac, renal or endocrine disease, current infections and medications.

Clinical data

1) Age and sex; 2) Mode of presentation: asymptomatic or symptomatic with ketosis or ketoacidosis; 3) Family history of type 2 diabetes and / or obesity; 4) Maternal history of gestational diabetes; 5) Blood pressure measurement: systolic blood pressure (SBP) and diastolic blood pressure (DBP); 6) Height, weight and body mass index (BMI). Standing height and weight were measured with the subjects in light clothing and without shoes. Height was recorded to the nearest centimeters and weight to the nearest 0.1 kg. The weighing scales (Detecto-Medic, New York, USA) were standardized daily using standard weights of 20 and 70 kg. Body mass index (BMI), defined as weight in kilograms per height (in meters) squared was calculated and used as an index for obesity; 7) Absolute waist circumference (AWC) as a measure of central (android) adiposity was taken at the mid point between umbilicus and xiphoid. Central adiposity is considered if WC > 88 cm in females, and > 102 cm in males ; 8) *Acanthosis Nigricans* (neck, axilla, elbow and back of knee); 9) Features of polycystic ovarian syndrome (PCOS): Hirsutism, graded according to Ferriman- Galloway scoring and menstrual irregularity which is defined as bleeding episodes occurring less than six cycles per year.

Biochemical Parameters

Fasting plasma glucose (FPG); Lipid profile: venous blood samples, collected without the use of a tourniquet, were analysed for fasting plasma glucose (FPG), serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), on an automated analyzer (Hitachi 911 analyser; Roche, Basle, Switzerland) with dedicated reagents supplied by Roche.

Blood glycated hemoglobin (HbA1c): was measured on a DCA 2000 analyser with dedicated reagent cartridge supplied by Bayer Corporation (Elkhart, IN, USA).

High sensitive C-reactive protein (hsCRP): was measured by immunoassay using monoclonal antibody coated with polystyrene particles. The assay was performed with a Behring BN-100 nephelometer (Dade Behring). The run-to-run coefficient of variation at CRP concentration ranging from 1.0 - 10 ug/ml was > 5%.

Urinary albumin / creatinine ratio: Fresh morning samples for measurement of urinary albumin and creatinine were obtained on three occasions from each subject and measured in a DCA 2000 analyzer with dedicated reagent cartridges supplied by Bayer. Patients were classified by urinary albumin: creatinine excretion ratio. Patients were classified as normoalbuminuric (urinary albumin : creatinine ratio < 30 mg/g), microalbuminuric (urinary albumin: creatinine ratio 30 – 300 mg/g), or macroalbuminuric (urinary albumin: creatinine ratio > 300 mg/g).

C peptide and insulin was measured by a solid phase I125 radioimmunoassay using the COAT, a count insulin kit from DPC (Diagnostic Products Corporation, Los Angeles, CA90045-5597 USA).

Serum testosterone (in females) was measured using competitive immuno-enzymatic assay on Beckman Access Immunoassay system.

Homeostasis Model assessment (HOMA) was estimated using the formula: FBG (mmol/l) X fasting insulin level (uU/ml) / 22.5^[11].

Islet cell Antibody (ICA) and Anti Glutamic Acid Decarboxylase (Anti GAD) was measured by validated commercially available ELISA assay (Combi Kit TG/TPO, Germany).

This study was approved by the local ethical committee

Statistical analysis

The data are presented as mean ± SD. Pearson correlation tests were used to assess the correlations and considered significant when p value was less than 0.05. The statistical analysis was carried out using the SPSS 12 for windows.

RESULTS

A total of 19 diabetic patients had fulfilled the inclusion criteria (12 female) with a mean age of 17.53 ± 1.4 years (Table 1). All patients with early onset type 2 diabetes were overweight ($n = 6, 30.8\%$) to obese ($n = 9, 69.2\%$) at diagnosis with a mean BMI of 31.43 ± 2.09 kg/m² and a mean absolute waist circumference of 94 ± 1.7 cm in females and 103.43 ± 1.24 cm in males. Hypertension was reported in three cases with mean systolic blood pressure (SBP) of 134.32 ± 8.45 and mean diastolic blood pressure (DBP) of 87.05 ± 10.34 mmHg respectively. The patients had wide spectrum of presentations from asymptomatic hyperglycemia in (57.9%), ketosis in (31.6%), and diabetic ketoacidosis in two patients (10.5%). Family history of type 2 diabetes was positive in 68.4% and maternal history of gestational DM was positive in 52.6%. 10 patients (52.6%) had acanthosis nigricans, a cutaneous marker of insulin resistance. Six female patients (out of 12) had clinical features of PCOS in the form of irregular menses and androgenic hirsutism. HOMA was found to have a strong positive correlation with BMI ($p < 0.001$), AWC in females ($p < 0.049$), TG ($p < 0.009$), DBP ($p < 0.01$) and a negative correlation with HDL-C ($p < 0.036$) and Apo A -1 ($p < 0.044$). HsCRP was also found to have a positive correlation with BMI ($p < 0.005$), AWC in females ($p < 0.035$) and males ($p < 0.001$), TG ($p < 0.001$), DBP ($p < 0.006$) and a negative correlation with HDL-C ($p < 0.026$).

DISCUSSION

Type 2 diabetes, characterized by insulin resistance and a relative decrease in insulin secretion, is traditionally a disease of adults. It is not common in the young and thought to be rare in children. Over the last two decades, it has been increasingly recognized in children and adolescence and is strongly associated with increased prevalence of obesity and insulin resistance^[12].

In our study, we found a typical insulin - resistant phenotype in these youngsters as evident clinically and biochemically (Table 1 and 2). This suggest that the phenomenon of increasing type 2 diabetes in adolescents may be a result of increasing obesity, in particular central adiposity, as a determinant of insulin resistance^[13].

There is a strong relationship between obesity and the development of insulin resistance in early adulthood^[14]. Puberty is a major cause of insulin resistance and insulin sensitivity decreases by ~ 30% during puberty with a compensatory increase in insulin secretion^[15]. Circulating levels of the insulin sensitizing adipocyte secretory product adiponectin were ~ 60% higher in white adolescent^[16]. HOMA-IR as a measure of insulin resistance, and hsCRP as a major acute phase

Table 1: Clinical characteristics of early onset type 2 diabetics at presentation

Characteristics	No. of Patients (N = 19)	%	Mean \pm SD
Age (years)			17.53 \pm 1.4
Sex			
Female	12	63.2	
Male	7	36.8	
Family history			
Present	13	68.4	
Absent	6	31.6	
Maternal history of Gestational DM			
Present	10	52.6	
Absent	9	47.4	
Presentation			
Hyperglycemia	11	57.9	
Ketosis	6	31.6	
DKA	2	10.5	
Body Mass Index (BMI) kg/m ²			31.43 \pm 2.09
Overweight	5	26.25	
Obese	14	73.75	
Waist circumference (cm)	-	-	
Females			94 \pm 1.7
Males			103.43 \pm 1.24
Systolic blood pressure (mmHg)	-	-	134.32 \pm 8.45
Females			132.24 \pm 6.9
Males			137.19 \pm 9.2
Diastolic blood pressure (mmHg)			87.05 \pm 10.34
Females	-	-	85.9 \pm 9.34
Males			89.32 \pm 9.89
Acanthosis nigricans			
Present	10	52.6	
Females	7	58.3	
Males	3	42.8	
Absent	9	47.4	
Features of PCOS (n = 12)			
Present	6	50	
Absent	6	50	
Diabetic complications			
Retinopathy	0		
Neuropathy	0		
Microalbuminuria	3	15.8	

protein and inflammatory marker showed variable degree of correlations with important components of the IRS (Table 3 and Graphs 1 and 2). Our results are consistent with other reports which showed positive correlations between fasting insulin level and blood pressure^[17], triglyceride^[18], and negative correlation with HDL-C^[19]. The metabolic difference observed can be explained by the relatively small sample studied together with the complex interplay of cultural / environmental and genetic factors in type 2 DM.

Certain ethnic groups show a particularly high prevalence of glucose abnormality among young persons, and diabetes prevalence appears to be increasing^[20]. This study shows that early onset type 2 DM is an emerging problem in Kuwait as a part of the accelerating epidemic in the world. In the United Arab Emirates, among those < 18 years, 12.5% persons with diabetes have type 2^[21]. A 10-country study in

Table 2: Results of laboratory investigations of early onset type 2 diabetics at presentation.

Laboratory Investigations	Mean + SD
Biochemical	
FPG (mmol/l)	13.03 ± 2.05
HbA _{1c} %	8.03 ± 0.71
TG (mmol/l)	2.38 ± 0.53
TC (mmol/l)	4.18 ± 0.79
LDL (mmol/l)	3.04 ± 0.59
HDL (mmol/l)	0.65 ± 0.13
TG:HDL Ratio	3.66 ± 0.49
APO-A1(gm/l) (N: 0.9-2.0)	1.66 ± 0.35
APO-B (gm/l) (N: 0.17-1.6)	0.82 ± 0.17
hsCRP (µgm/ml)	3.89 ± 0.49
	Low risk < 1.0
	Medium risk 1-3
	High risk > 3.0)
Urinary albumin	Normal in 16 patients (84.25%)
Creatinine ratio (mg/gm)	Microalbuminuria in 3 patients (15.75%)
Elevated ALT	In 4 patients (21%)
Hormonal	
C-peptide (p mol/l) (N: 256 - 1325)	924.362 ± 5.8
Fasting Insulin (µIU/ml) (N < 22)	21.56 ± 3.78
HOMA-IR (N < 3.2)	11.78 ± 1.8
Testosterone in females (pmol/l) (N: 0.2-2.98)	2.61 ± 0.38
Immunological	
Anti Glutamic Acid Decarboxylase(AGAD):	Negative
Islet cell antibody (ICA):	Negative

Asia has shown ~ 10% of young people with diabetes attending major centers having type 2 diabetes, with considerable regional variation^[22]. The prevalence of diagnosed diabetes among American Indians aged 15 – 19 years in the southwestern U.S increased from 3.2 to 4.5 per 1,000 from 1990 to 1997^[23]. Interestingly, the number of cases who presented with early onset type 2 diabetes (19 cases), during the two-year-period between 2005 - 2006 represent a significant percentage compared to the number of cases with type 1 diabetes (32 cases), which represents 37% of new cases of young diabetic patients. This is consistent with other reports. In Japan, cases with early onset type 2 outnumber the new cases of type 1 diabetes diagnosed annually. In the US, early onset type 2 diabetes now accounts for 8 - 45 % of new cases of young diabetics^[12].

Family history plays a crucial role, with more than two-thirds of patients with type 2 diabetes having at least one parent suffering from type 2 DM, and an even greater frequency with two parents having type 2 diabetes among Pima Indians aged 5 - 19 years^[24]. Gender is also important as 63.2% of our patients are females. Girls are 1.7 times more likely than boys to develop type 2 DM in an analysis of a large set of studies^[6]. Maternal history of gestational diabetes was found in more than 50% of our patients. Exposure *in-utero* to a mother with gestational diabetes is particularly associated with increased risk

Table 3: Pearson Correlations between HOMA and hsCRP with different components of metabolic syndrome

	HOMA-IR	p-Value	hsCRP	p-Value
BMI	0.709	(0.001)**	0.615	(0.005)**
WC Female	0.578	(0.049)*	0.610	(0.035)*
WC Male	0.669	(0.1)	0.977	(0.001)**
SBP	0.364	(0.125)	0.149	(0.593)
DBP	0.573	(0.01)**	0.602	(0.006)**
TC	0.096	(0.696)	0.098	(0.688)
TG	0.579	(0.009)**	0.824	(0.001)**
HDL-C	-0.485	(0.036)*	- 0.508	(0.026)*
TG : HDL-C	0.563	(0.02)*	0.89	(0.671)
LDL-C	0.306	(0.203)	0.072	(0.769)
Apo A1	-0.467	(0.044)*	- 0.278	(0.249)
Apo B	-0.154	(0.529)	- 0.224	(0.357)

Values are mean ± SD; *Significant (p < 0.05); ** Highly significant (p < 0.01)

of diabetes and appears to decrease insulin secretory capacity rather than decreasing insulin action^[25]. Also, those persons with lowest birth weight and highest prepubertal body weight are particularly at risk of insulin resistance and diabetes^[4, 26].

Early onset type 2 DM appears to be an aggressive disease from the cardiac standpoint. Several studies showed increased prevalence of premature coronary heart disease (CHD) in young population^[27,28,1] as biomarkers of increased risk of adverse cardiovascular outcomes such as lipids, hsCRP and microalbuminuria are already present in these youngsters. Fibrous plaque lesions are present in the aorta and coronary arteries of children and young adults and associated with obesity, dyslipidemia, and cigarette use^[28]. Risk factors for cerebrovascular disease (CVD) predate the onset of type 2 diabetes in adults, but there are no prospective studies on CVD risk factors and long-term outcomes in childhood and adolescent type 2 DM. The American Diabetes Association has recently proposed that desirable levels of LDL for children and adolescent without and with diabetes be considered < 130 and < 100 mg/dl, respectively^[29].

In this study, microalbuminuria as a marker of cardiovascular disease was seen in 15.75% of our patients at diagnosis. In another study microalbuminuria was found in 22% at diagnosis and in 58% at follow-up, macroalbuminuria in 0 and 16%, and hypercholesterolemia in 18 and 30%, suggesting the tendency to progression of both micro- and macrovascular disease^[30]. In another study of 178 Pima Indians with early onset of type 2 DM before age 20, a urinary protein-to-creatinine ratio > 0.5 g/g was seen in 20% after 25 years, implying a similar relationship between duration of diabetes and nephropathy to that seen in person with adult onset of diabetes, while there was relative protection against retinopathy, which had developed in 15% cases only^[31].

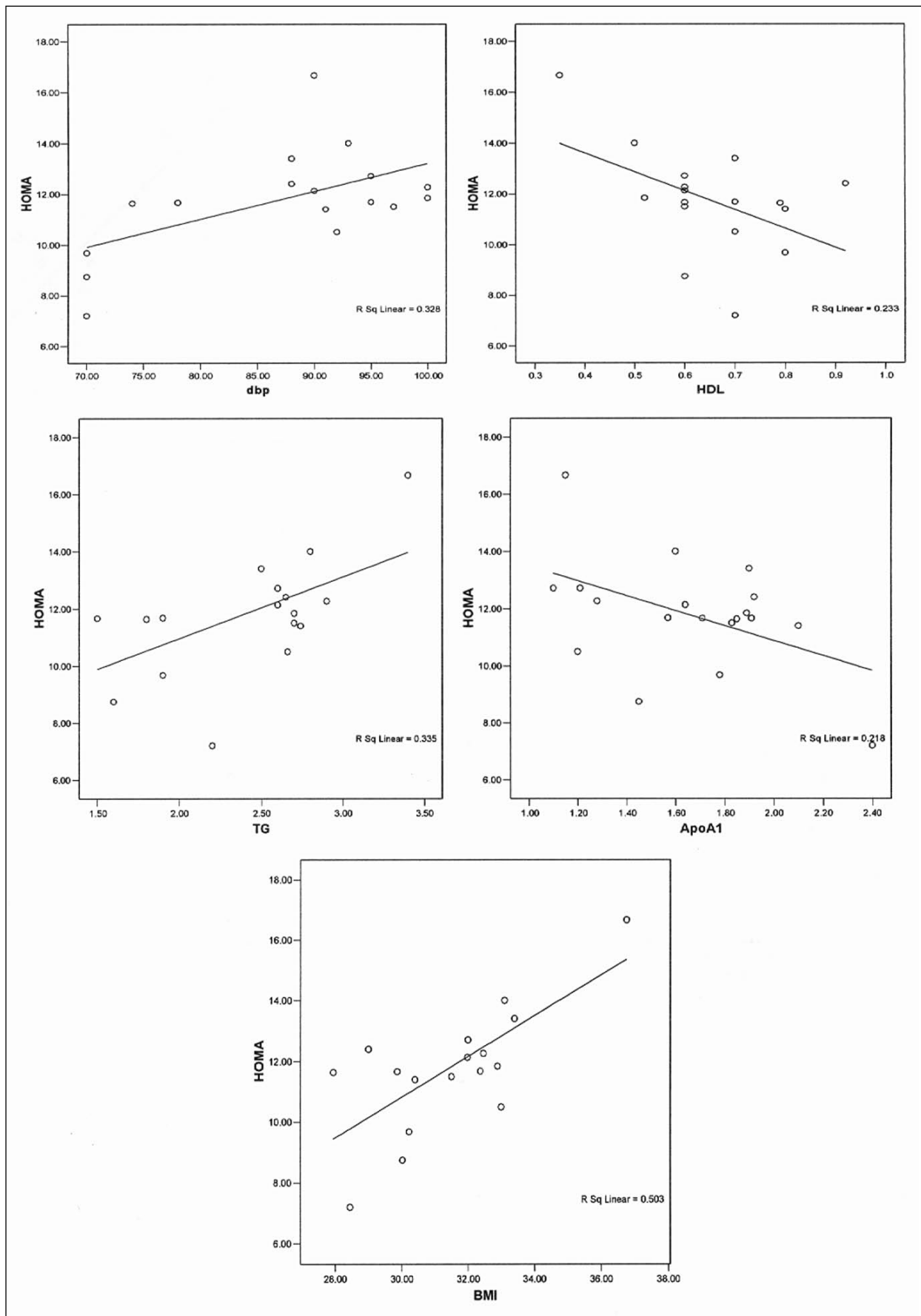


Fig. 1: Correlation between Homeostasis model assessment (HOMA-IR) and different components of metabolic syndrome

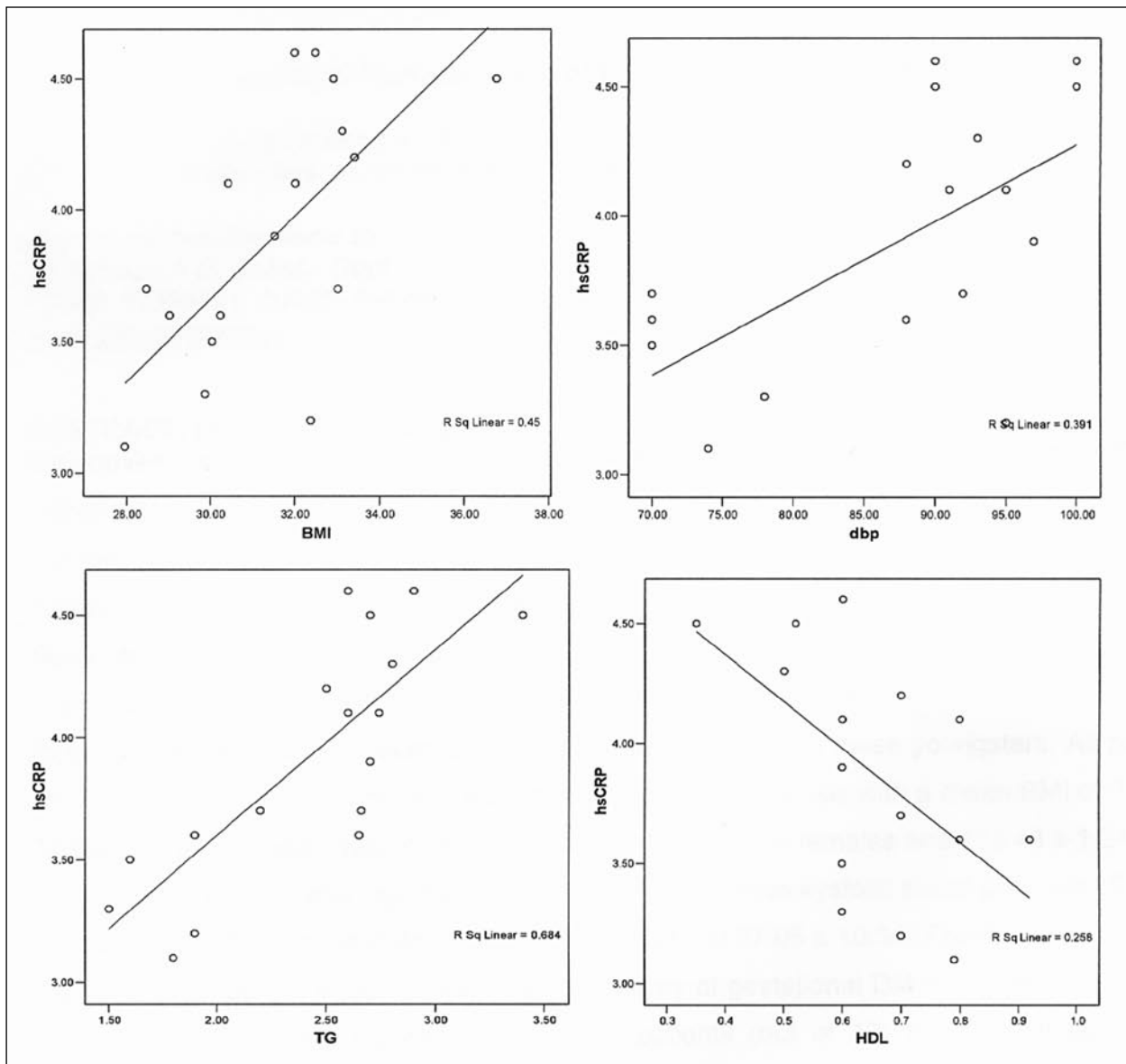


Fig. 2: Correlation between high sensitive C - reactive protein (hsCRP) and different components of metabolic syndrome.

Microalbuminuria measurement at diagnosis and yearly thereafter, as well as ACE inhibitor treatment for patients with microalbuminuria or hypertension, appears appropriate, with recognition of the potential teratogenicity of these agents in young women.

Of particular importance, mean HbA1c was found to be $8.03 + 0.71$ (minimum 7.2%, and maximum 10.2%). This high standard deviation and wide difference between minimum and maximum values of HbA1c reflects the wide spectrum of presentation of type 2 diabetes in this young age group, from asymptomatic to severely symptomatic with ketosis and occasionally ketoacidosis. Consequently, there may be underestimation of the magnitude of type 2 diabetes in youth because of under diagnosis with no or few symptoms or misclassification as type 1 DM for those patients who presents with more severe

hyperglycemia. The likelihood of under diagnosis for lack of symptoms can be appreciated from the Japanese studies, where the mean HbA1c of those found at screening was 7.9%, with 46% having levels < 6.5%, while those presenting with symptoms had mean HbA1c at diagnosis of 10%^[32].

Screening for type 2 in young patients appears to be an appropriate target in this age group as it meets a number of criteria. The disease is common, exhibits prolonged latency without symptoms, serious in terms of morbidity and mortality, and can be assessed simply by blood glucose measurement with acceptable sensitivity and specificity. Furthermore, a number of interventions can prevent or delay disease onset, and it may be more effective to treat diabetes early in order to delay or prevent the complications. The consensus position of the American Diabetes Association^[33] and

the American Academy of Pediatrics^[7] recommends targeted screening at age > 10 years or onset of puberty for those with BMI above the 85th percentile, who have the following risk factors: positive family history, ethnic origin and signs of insulin resistance.

In this study, we found that four out of 19 patients (21%) had mildly elevated alanine aminotransferase (ALT) (1 - 2 times upper limits of normal). Recent studies^[34,35] suggest significant elevation of aminotransferases in obese children and adolescents. Park *et al*^[34] investigated the relation between non-viral or non-alcoholic elevation in ALT and the metabolic syndrome in Korean adolescents. Several components of metabolic syndrome were significantly worse in the group with elevated ALT concentration. A significant correlation existed between elevated ALT and abdominal obesity, high TG concentration, and low HDL concentration. In another study, Yoo *et al*^[35] observed a significant correlation between ALT and HOMA-IR. In a most recent study^[36], adoption of sex-related cut-off of ALT levels has been suggested for the pediatric and adolescent population.

The further metabolic derangement of PCOS which was found in half of our female patients, is frequently seen in type 2 diabetics. PCOS is associated with decreased glucose disposition; with ~ 30% of adolescent girls with PCOS having IGT and 4% having type 2 DM^[37,38]. Adolescents with PCOS who develop IGT have similar degrees of obesity and elevations in circulating testosterone to those with normal glucose tolerance but show blunting of first-phase insulin secretion in response to intravenous glucose with a consequent decrease in the glucose disposition index^[39].

CONCLUSION

Awareness among physicians that type 1 DM is not the only form of diabetes in the young is an important practical issue. Type 2 DM is frequently asymptomatic and should be considered in obese adolescents from at-risk ethnic groups who have a positive family history of DM. As upto 10% of these patients may present in ketoacidosis, it is possible that some patients with type 2 diabetes may be misclassified or thought to have type 1 diabetes and commenced on insulin from diagnosis with aggravation of their obesity and insulin resistance. There is an urgent need for community-based screening programs and also for studies on primary and secondary prevention of complications.

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Original Article

The Value of Transesophageal Echocardiography to Detect Coronary Artery Stenosis in Children

Mustafa A Al-Qbandi¹, Jeffrey Smallhorn²¹Department of Pediatrics and Congenital Heart Diseases, Chest Disease Hospital, Kuwait²Division of Cardiology, Department of Pediatrics, The Hospital for Sick Children and the University of Toronto, Ontario, Canada

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ABSTRACT

Objective: To assess the utility of transesophageal echocardiography (TEE) in the detection of proximal coronary artery (CA) stenoses in children undergoing cardiac surgery

Design: Longitudinal cohort study conducted between January 2000 and April 2008

Setting: Chest Diseases Hospital, Kuwait and the University of Toronto, Canada.

Subjects: Fifteen patients of either sex, aged between three days to 17 years (median = 8 years, 8 female) identified as having proximal CA stenosis by TEE

Interventions: Pre and postoperative TEE done in all patients where CA surgery was performed

Main Outcome Measures: Patients with proximal CA Doppler and color flow patterns suggestive of proximal CA stenosis after cardiac surgery were identified. The clinical, echocardiographic, angiographic and autopsy data were reviewed.

Results: We identified with TEE proximal CA stenoses after Ross-Konno (5/15), arterial switch repair (2/15), repair of supra-avalvar AS (2/15), reimplantation of ALCA (2/15), complex AV and sub-AV stenosis (1/15), isolated supra-avalvar PS (1/15), post-Norwood stage I (1/15) and redo of RV to PA conduit (1/15). RCA stenoses were identified in nine and LCA stenoses in six cases. Six cases had anomalous origin of CA diagnosed preoperatively. Three Doppler flow patterns were identified. Wall motion abnormalities were seen in all cases. The result of TEE of CA's altered immediate surgical management in eight patients.

Conclusion: TEE imaging and Doppler interrogation of the proximal CAs reliably detects stenoses and may provide important information leading to surgical revision of the CA anastomoses. We suggest routine perioperative TEE assessment of proximal CA anastomoses following surgical reimplantation.

KEY WORDS: children, coronary arteries, transesophageal echocardiography

INTRODUCTION

The majority of surgical procedures for congenital heart disease do not result in compromise to the coronary circulation. There are a few but important cardiac operations that may directly or indirectly affect the coronary arteries. Most commonly these involve the arterial switch operation, Ross procedure, repair of supra-aortic valve stenosis, or reimplantation of an anomalous coronary artery origin with or without an intramural course. In rare instances external compression of the right coronary artery by a right ventricle to pulmonary artery conduit^[1] or isolation of the right or the left coronary artery by a deformed coronary cusp may compromise the coronary circulation^[2-7]. In general, it is difficult for the surgeon to determine by visual inspection if coronary artery stenosis is the cause for acute cardiac failure in the immediate postoperative period. More recently transesophageal echocardiography (TEE)

has been utilized to assess coronary artery anatomy and function, thus providing the surgeon with an intraoperative tool to evaluate this component of the repair.

This study reports a heterogeneous group of patients in whom TEE played an important role in the evaluation of coronary artery anatomy and function following repair of a variety of congenital heart defects.

SUBJECTS AND METHODS

This study was conducted in Canada during the period of 2000 - 2008, at the Hospital for Sick Children, Toronto. Patients who were born with congenital heart disease and their surgery involved coronary artery repair and/or transfer were recruited. During the period of 2000 - 2008, 15 cases of proximal coronary artery stenoses were identified in this hospital. The first five years of the study involving 12 patients

Address correspondence to:

Dr. Mustafa A. Al-Qbandi, DCH, FAAP, FRCPC, FSCAI, Department of Pediatric and Congenital Heart Diseases, Chest Disease Hospital, P O BOX 4082, Safat, 13081, Kuwait. Tel: +965-4829613, Fax: +965- 4829613, E-mail: jarrah5@hotmail.com

Table 1: Summary of the procedures at our institution

Procedure	Total number	
	Jan 2000-Apr 2008	(number=CA involved)
Ross-Konno	23	5 (4 = RCA, 1 = LMCA)
Arterial switch	151 (single CA = 5)	2 (2RLCx, one intramural)
SAV stenosis	21	2 (2 = RCA)
RV-PA conduit	137	1
Norwood stage I	93	2 (1 = pre-coronary, 1 = LMCA occlusion)
Traumatic/congenital	1	1
ALCA-PA	1	1
ALCA-RAS	1	1
Aortic valve stenosis	1	1

ALCA-PA= anomalous left coronary artery from pulmonary artery, LMCA= left main coronary artery, RAS= right aortic sinus, RCA= right coronary artery, RV-PA conduit= right ventricle, to pulmonary artery conduit, SAV= supra-aortic valve stenosis

was prospective. The remaining cases were collected from our data base over a period of three years. Table 1 shows different types of surgeries involving coronary arteries at Sick Kids Hospital. It is a routine practice at hospital to perform pre-and postoperative transesophageal echocardiography in all patients with complex congenital heart diseases, especially if coronary arteries were involved. Both pediatric and adult TEE probes were utilized depending on patients' age and/ or weight. A Hewlett Packard (HP 5500) imaging system utilizing high frequency transducers was used in all cases. A complete 2D-echocardiography and Doppler interrogations of proximal coronary arteries was done in the pre and postoperative period. Doppler velocity profiles, color flow patterns and wall motion abnormalities were recorded. The results were communicated to the surgeon immediately. A normal coronary artery pattern is one with a flow velocity not exceeding 50 cm/sec, with a dominant diastolic pattern. It is important to remember that a Doppler angle as close to zero degree as possible is important for the velocity data to be valid. An abnormal flow pattern appears to be one with either biphasic high velocity flow of more than 50 cm/sec, an increase in the systolic phase compared to that in diastole or the presence of systolic flow reversal.

This study was approved by the local hospital ethics committee.

RESULTS

Clinical course and outcome

Stenoses of the proximal right coronary artery system were encountered in nine patients, while in six cases it involved the left coronary artery (one diagnosed with fibro-intimal proliferation of the coronary arteries at autopsy). An intraoperative diagnosis of coronary stenosis was made in eight cases, which affected surgical management. A later postoperative diagnosis

was made in seven cases (Table 2).

Two cases also had a preoperative TEE diagnosis of proximal coronary artery obstruction both of whom had evidence of residual coronary artery stenosis in the immediate postoperative period (case 1 and 5). In case 1, the diagnosis of isolation of the left main coronary by a deformed left coronary cusp was made (Fig. 1). The Doppler flow pattern showed reversed color flow in the main and in the left anterior descending coronary arteries. The patient underwent a Ross-Konno procedure and had intraoperative evidence of right coronary artery stenosis that was subsequently repaired. In case 5, the echocardiographic diagnosis was ALCA from the right anterior sinus with evidence of an interarterial / intramural stenotic segment. The patient underwent re-implantation of the left main coronary artery with Doppler and autopsy evidence of left main coronary artery stenosis.

Three patients received coronary vessel grafts (cases 8, 14 and 15) with only one (case 15) having a saphenous vein graft for proximal coronary artery stenosis. This graft was compressed by an RV-PA conduit, which was inserted for severe pulmonary valve stenosis in a criss-cross heart. Stent implantation of the stenotic segment was successful (Fig. 2). The other two cases had internal mammary artery grafts, one of whom had evidence of sinus node dysfunction following distal right internal mammary artery graft.

Cardiac transplantation was performed in two cases following failure of the initial repair (cases 7 and 10). In case 7, following a Ross-Konno procedure for tunnel left ventricular outflow tract obstruction, there was TEE evidence of severe left main coronary artery stenosis (Fig. 3) which was confirmed at autopsy. The explanted heart showed that both coronary arteries were normally located with narrowing of the ostia and dilated distal vessels. The left main coronary take-off was very acute with microscopic evidence of severe (80-90%) fibro-intimal proliferation, which was confined to within the first centimeter of both coronary arteries. The myocardium demonstrated extensive hemorrhagic myocardial necrosis, which was attributed to the severe coronary ostial stenosis. In case 10, the patient had a pre-existing single coronary artery with a small retro aortic left main coronary artery. Following aortic and mitral valves repair, and aortic arch repair, the patient had two cardiac arrests and irreversible ventricular dysfunction. Autopsy of the explanted heart revealed: diffuse endocardial fibroelastosis involving the left-sided chambers, a bicuspid aortic valve, an adequate aortic arch and a small mitral valve. The coronary arteries demonstrated fibro-intimal proliferation, focal fragmentation and duplication of the internal elastica which involved the left to a greater extent.

Coronary artery stenosis following an arterial switch operation was seen in two cases (3 and 11, Fig. 4). In both, the ventricular septum was intact and the

Table 2: Summary of the cases with coronary artery stenoses

	Sex	Age	Time of Diagnosis	Diagnosis	Surgery	Pre/ Post-operative findings	Outcome & follow-up
1	F	20 days	Intraoperative	Severe AR, EFE, dilated cardiomyopathy	Ross-Konno procedure	Preop: isolation of LMCA Intraop: proximal RCA stenosis	Redo CA button
2	M	28 days	Intraoperative	Shone's complex	Aortic valvotomy, arch reconstruction, followed by Ross-Konno procedure	Proximal RCA stenosis	Dead Autopsy: posterior RV wall infarction
3	F	1 year	Intraoperative	TGA/IVS (2RLCx)	Arterial switch operation	Proximal RCA stenosis	Redo button. Abnormal DSE
4	M	1 year	Intraoperative	Non William's supra-aortic valve stenosis	Repair of SAV stenosis	Proximal RCA stenosis	Mild proximal RCA stenosis
5	F	4 years	Intraoperative	ALCA from right aortic sinus with an intramural, interarterial stenotic segment	Pericardial patch reimplantation of LMCA to left aortic sinus	Preop: stenotic intramural segment Postop: stenotic reimplanted LMCA Dead	
6	F	10 years	Intraoperative	Critical aortic valve stenosis	Ross procedure	Tear in Cx, proximal LAD stenosis	Patch reconstruction of LMCA-circumflex
7	M	16 years	Intraoperative	Tunnel left ventricular outflow tract obstruction	Ross-Konno procedure followed by cardiac transplantation	Proximal LMCA stenosis	Native heart=80-90% fibrointimal proliferation of both CA's. Cardiac transplantation
8	F	12 years	Intraoperative	Shone's complex variant & single coronary artery	Modified Konno & artificial aortic valve	Occlusion proximal RCA	Dista RIMA to RCA
9	F	6 months	Postoperative	HLHS	Norwood stage I	Complete occlusion of LMCA	Tricuspid valve annuloplasty, BDCPA
10	M	1.5 years	Postoperative	Shone's complex	Aortic valvotomy, arch & MV repair	Single CA, long retroaortic LMCA, small LAD & Circumflex	Native heart = fibrointimal proliferation of CA's. Cardiac transplantation
11	M	7 years	Postoperative	TGA/IVS (2RLCx, Intramural coronary artery)	Takeuchi procedure	Tunnel stenosis-LMCA stenosis	Redo LMCA-Tunnel
12	F	9 years	Postoperative	Williams syndrome	Repair of SAV stenosis	Proximal RCA stenosis	No significant ST changes
13	F	15 years	Postoperative	ALCA from pulmonary artery	Re-implantation of LCA	Proximal LMCA stenosis	Possible stent
14	M	16 years	Postoperative	Pulmonary & suprapulmonary valve stenosis	Traumatic or congenital	Occlusion proximal RCA	RIMA graft
15	M	17 years	Postoperative	Criss-Cross heart, pulmonary valve stenosis	RV-PA conduit	Proximal RCA stenosis	Saphenous vein graft followed by RCA stenting

ALCA = anomalous left coronary artery, AR = aortic regurgitation, CA = coronary artery, DSE = dobutamine stress echocardiography, EFE = endocardial fibroelastosis, F = female, LAD = left anterior descending, HLHS = hypoplastic left heart syndrome, LMCA = left main coronary artery, IVS = intact ventricular septum, M = male, MV = mitral valve, RCA = right coronary artery, RIMA = right internal mammary artery, RV-PA = right ventricular to pulmonary artery, TGA = transposition of great arteries

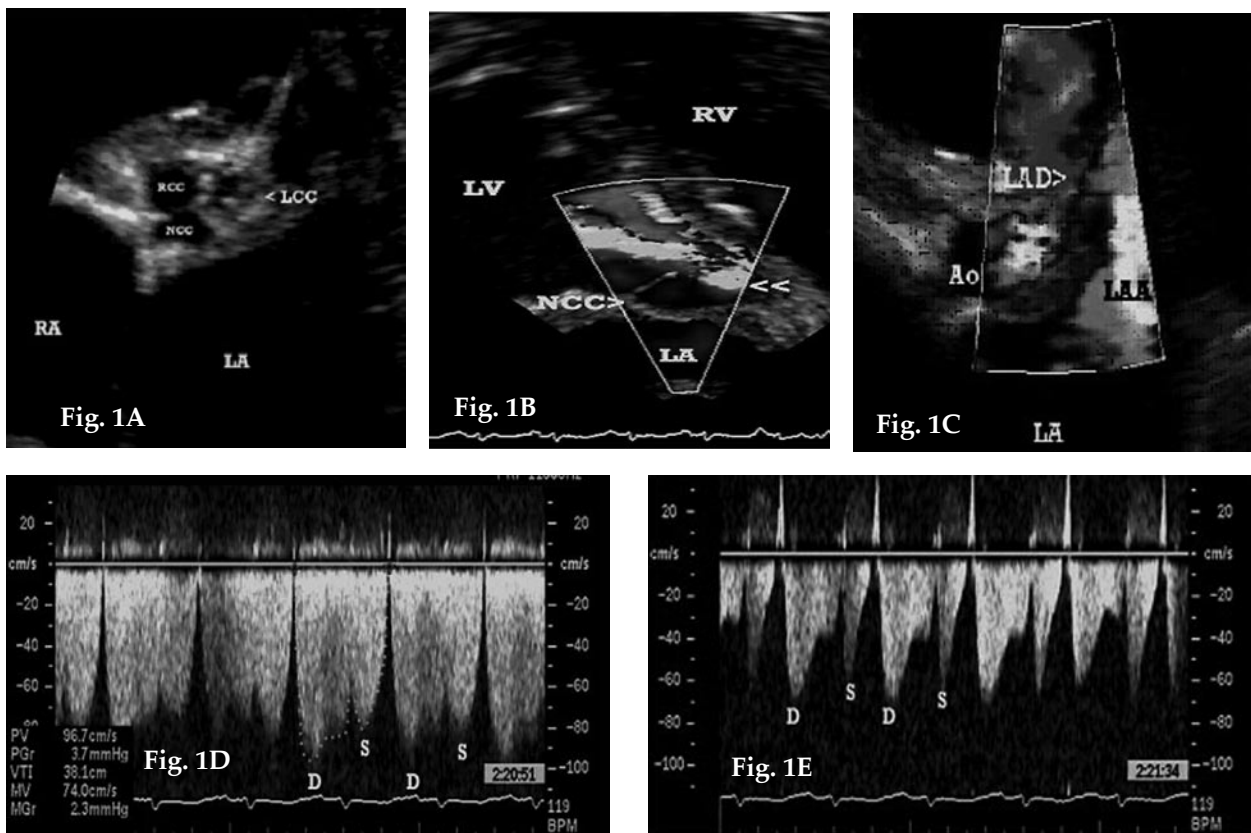


Fig. 1: Isolation of the left main coronary artery: (A) A transthoracic short axis view at the level of the aortic valve showing a normal right and a non-coronary cusps (RCC, NCC), but deformed left coronary cusp (LCC, arrowhead). RA=Right atrium, LA=Left atrium. (B) Preoperative transesophageal echocardiogram at the level of mid-esophagus showing moderate-to-severe aortic valve regurgitation starting above the non-coronary cusp at the site of the deformed left coronary cusp (double arrow). RV= right ventricle, LA= left atrium, LV= left ventricle. (C) Color spectral flow signal in the left main coronary artery. There is a reversal color flow in left anterior descending (LAD) coronary artery (blue instead of red color). (D) Intraoperative pulsed Doppler spectral flow signal in the right coronary artery showing non-phasic high velocity signals in diastole (D) and systole (S) with a velocity of 96.7cm/sec (mean gradient of 2.3 mmHg). LAA=Left atrial appendage. (E) Readjustment of the right coronary artery button resulted in biphasic low velocity signals with a peak in diastole of 65 cm/sec.

coronary artery patterns were 2LRCx. In case number 3 the right coronary artery stenosis was evident and redo of the button was performed. In the other patient, the left main coronary artery was intramural and a modified tunneling of the coronary artery was performed. Transesophageal Doppler color flow revealed turbulence at the junction of baffle and left coronary artery. Cardiac catheterization confirmed supra-valvular pulmonary stenosis and stenosis at the baffle left coronary artery junction with a 95% stenosis of the proximal LMCA. Revision of the Takeuchi flap and unroofing of the LCA were undertaken. On follow-up, there was mild hypokinesia of the inferior left ventricular wall that did not improve during a dobutamine stress test. A recent cardiac catheterization revealed widely patent coronary arteries and the Takeuchi flap baffle.

Supra-aortic valve stenosis was encountered in two cases (4 and 12) with one being associated with William's syndrome. In both cases, there were evidences of right coronary artery stenosis. This was confirmed in both cases by a postoperative angiogram; however,

it was felt to be too mild for further intervention.

Late onset of proximal coronary artery stenosis following re-implantation of the left main coronary artery for ALCA-PA was seen in one case (case 13). Nine years following repair a dobutamine stress echo revealed hypokinesia of the apical septum with dyskinesia of the mid-anteroseptal region, base of the septum and mid-anterior free wall. This was present at rest, did not improve with low dose dobutamine and was persistent at peak stress. There was a sub-optimal increase in ejection fraction and blood pressure (EF - 66 to 68%), with a 2-3 mm ST depression in LI, II, V4-V6. A TEE demonstrated normal flow in the RCA, but turbulent color flow in the proximal LMCA. At angiography the right coronary artery was normal, but the LMCA was diffusely smaller at its proximal take off with some dilatation just prior to bifurcating into the left anterior descending and circumflex. This case is currently being followed as recommended by our adult cardiology colleagues.

In case 6, during a Ross-Konno procedure for severe postoperative aortic regurgitation there was an injury

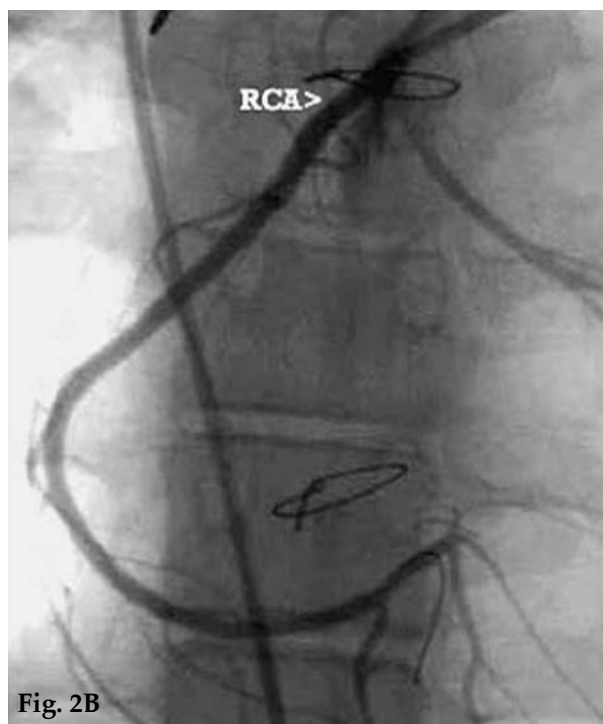
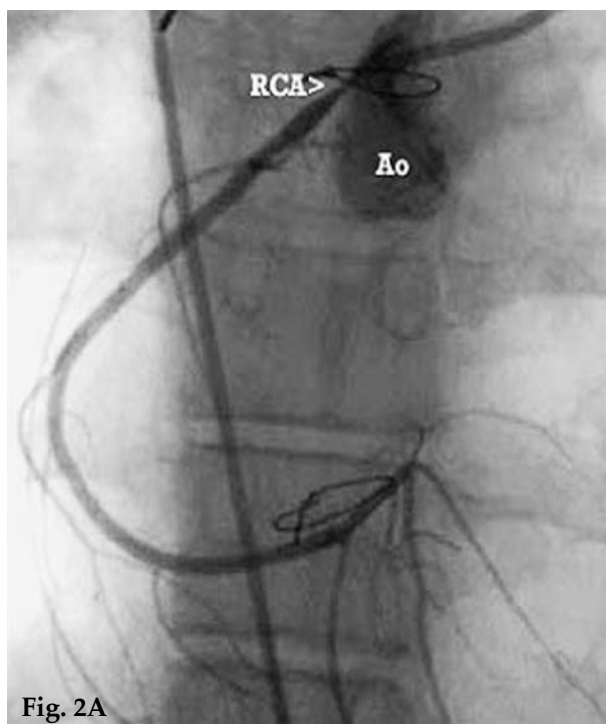


Fig. 2: Right ventricular to pulmonary artery external conduit in a patient who had a diagnosis of criss-cross heart and severe pulmonary valve stenosis: (A) Pre-stent placement, showing proximal right coronary artery stenosis. RCA=Right coronary artery. (B) Post-stent placement, with very good results.

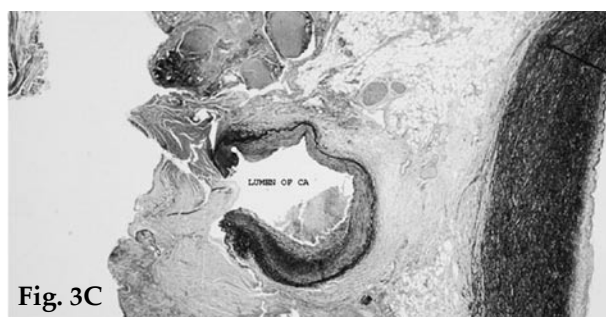
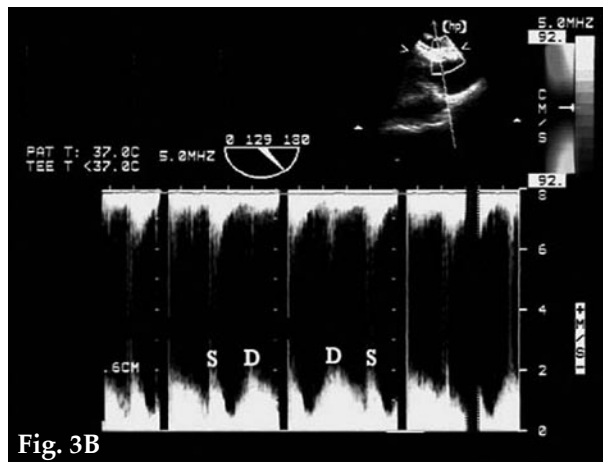
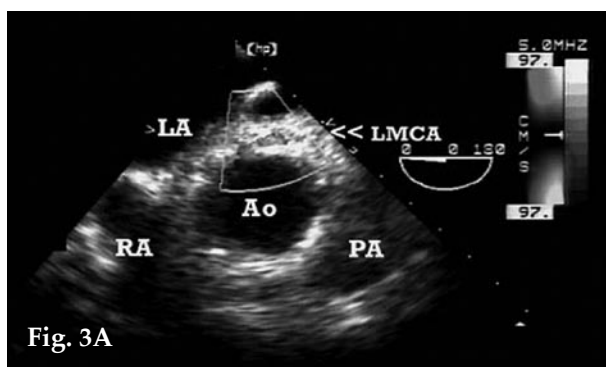


Fig. 3: Left ventricular outflow tunnel obstruction (Post Ross-Konno procedure): (A) Proximal left main coronary artery (LMCA) showing color Doppler flow aliasing. LA=Left atrium, RA=Right atrium, PA=Pulmonary artery. (B) Spectral Doppler flow pattern of the same vessel with a peak instantaneous gradient of 20 mmHg. The child had a complete heart block at the time of surgery (arrow head indicates ventricular pacing). (C) Shows histology picture of coronary artery fibroelastosis leading to coronary artery stenosis.

to the circumflex coronary artery. A left main coronary artery arterioplasty (patch reconstruction) was done. An intra-operative TEE demonstrated laminar flow in the LAD and circumflex, a very small right coronary artery with no wall motion abnormalities. A follow-up echocardiogram performed several months

later demonstrated reduced left ventricular ejection fraction and segmental wall motion abnormalities in the distribution of the left coronary. A subsequent angiogram suggested kinking of the left main coronary artery. The echocardiogram showed similar findings to the angiogram. However, the flow in the left main,

Table 3: Summary of transesophageal echocardiography (TEE) parameters in cases with coronary artery stenosis

Case	Diagnosis	Wall motion abnormalities	Color Doppler	Spectral Doppler pattern	Peak diastolic velocity(cm/sec)
1	Severe AR, EFE, dilated cardiomyopathy	Mild RV free wall hypokinesia	RCA: turbulent color flow	Biphasic high velocity signal in D&S	96.7
2	Shone's complex	Severe IVS/RV/LV dyskinesia	RCA: turbulent color flow	Mild increase D flow, S reversal flow	60
3	TGA (2RLCx)	LV: inferior & inferoseptal wall hypokinesia	RCA: turbulent color flow	Biphasic high velocity signal in D&S	180
4	Non William's supra-aortic valve stenosis	IVS dyskinesia	RCA: turbulent color flow	Mild increase D flow, S reversal flow	50
5	ALCA from right aortic sinus with an intramural, interarterial stenotic segment	Severe dyskinetic IVS & LV free wall	LMCA:turbulent color flow	Biphasic high velocity in D&S	150-180
6	Critical aortic valve stenosis	LV: anterior & inferior septum dyskinesia	LMCA: turbulent color flow	Not obtained	Not obtained
7	Tunnel left ventricular outflow tract obstruction	Dyskinetic IVS & LV free wall	LMCA: turbulent color flow	Biphasic high velocity in D&S	200
8	Shone's complex variant & single coronary artery	Decreased RV function, paradoxical septal motion & reduced RV free wall motion	RCA: no color flow demonstrated	Not obtained	Not obtained
9	HLHS	Hypokinetic basal IVS	LMCA: no color flow	Diastolic reversal flow in distal LAD, increased. Biphasic flow in RCA	RCA=80
10	Shone's complex	IVS dyskinesia	LMCA: normal color flow	Mild increase D flow, S reversal flow	70
11	TGA (2RLCx, Intramural coronary artery)	LV: inferior&inferoseptal wall hypokinesia	LMCA-Tunnel: turbulent color flow	Not obtained	Not obtained
12	Williams syndrome	RV wall & IVS dyskinetic	RCA: turbulent color flow	Mild increase D flow, S reversal flow	70
13	ALCA from pulmonary artery	LV: apical setal hypokinesia & dyskinesia of midanteroseptal, base of septum	LMCA: turbulent color flow	Mild increase D flow, S reversal flow	50
14	Pulmonary & suprapulmonary valve stenosis	Akinesia of distal IVS	RCA: no color flow demonstrated	Not obtained	Not obtained
15	Criss-Cross heart, pulmonary valve stenosis	Hypokinetic basal & midinferior RV wall / IVS	RCA: no color flow demonstrated	Not obtained	Not obtained

ALCA = anomalous left coronary artery, AR = aortic regurgitation, D = diastole, EFE = endocardial fibroelastosis, LMCA = left main coronary artery, LV = left ventricle, HLHS = hypoplastic left heart syndrome, IVS = interventricular septum, RCA = right coronary artery, RV = right ventricle, TGA = transposition of great arteries, S = systole

anterior descending and circumflex was low velocity and laminar. A dobutamine stress echo performed at the time of the angiogram demonstrated improvement of global and segmental LV function both at rest and with low dose and peak stress. She is currently asymptomatic and is maintained on aspirin.

We have encountered one case of coronary artery obstruction following Norwood stage I for hypoplastic left heart syndrome (case 9). In retrospect, the patient

had stormy postoperative course and tricuspid valve regurgitation that was not explained. Her TEE at the time of initial surgery did indeed show reversal diastolic flow in left main coronary artery that was missed. The patient subsequently underwent bi-directional cavopulmonary anastomosis and tricuspid valve annulopalsty. Postoperative TEE showed complete occlusion of the left main coronary artery, with diastolic reversal flow in left anterior

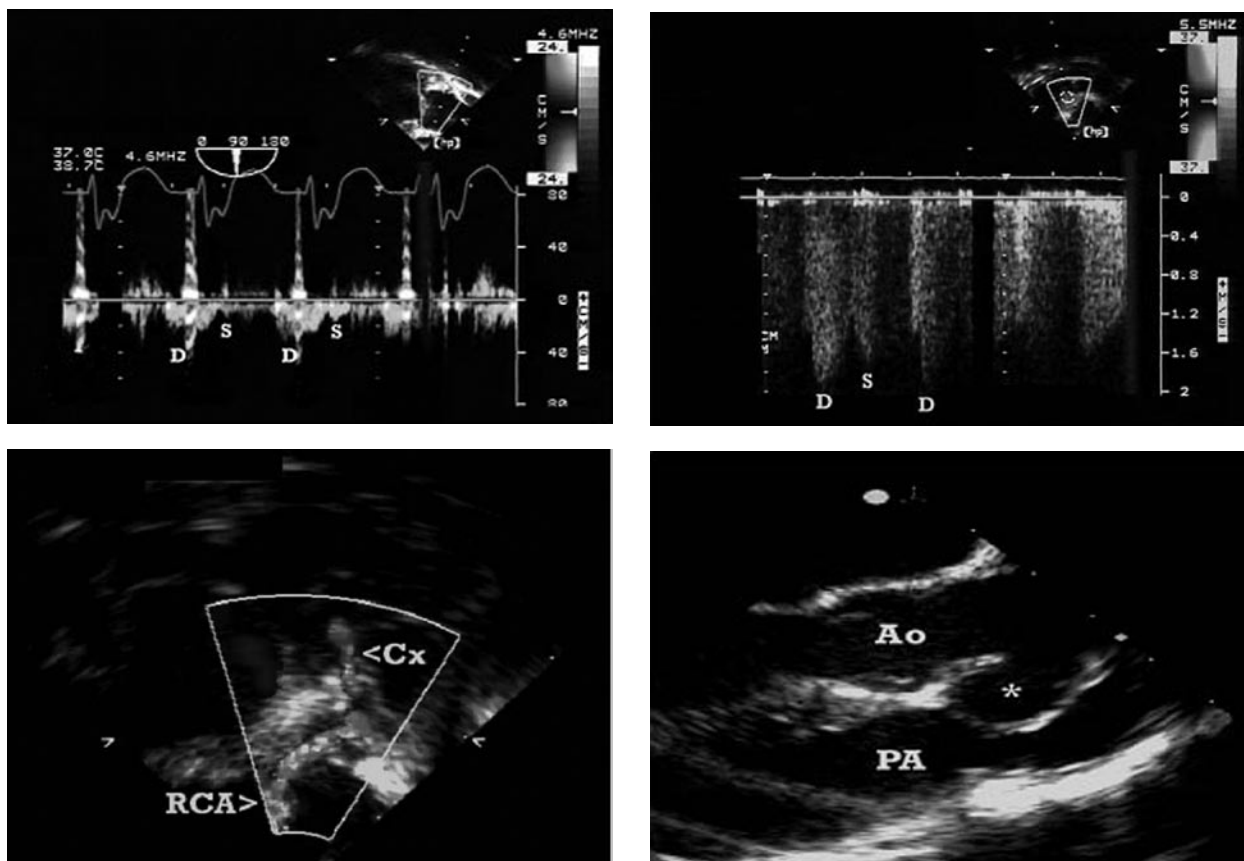


Fig. 4: Transposition of great arteries (TGA): (A) A normal pulsed Doppler spectral flow signal in the right coronary artery with low biphasic flow velocity signals in a patient with transposition of the great arteries- TGA (1LCx2R). (B) Pulsed Doppler spectral display in the right coronary artery (RCA) in a patient with TGA demonstrating a high velocity signals which are non-phasic with a peak diastolic velocity of 2cm/sec. (C) Color Doppler flow mapping in the same patient with RCA stenosis, shown as the mosaic yellow and red color in the narrowed proximal segment representing high-velocity flow as distinct from the blue color representing laminar flow more distally. (D) TGA with intramural left main coronary artery (LMCA) who underwent Tacheuchi procedure. A 2D-Image and Color Doppler flow mapping revealed aliasing at site of tunnel-LMCA junction. (PA = Pulmonary artery)

descending coronary artery. The right coronary artery showed an increased biphasic flow velocity reaching to a maximum of 80 cm/sec. There was also mild hypokinesia of the basal interventricular septum. The findings were confirmed at cardiac catheterization.

Finally, two of our cohort patients died in the immediate postoperative period (case 2 and 5). In case 2, the patient was diagnosed with severe aortic valve stenosis for which he required balloon valvuloplasty. A Ross-Konno procedure was then performed for severe aortic valve regurgitation. TEE intraoperative revealed evidence of right-sided coronary artery stenosis. At autopsy, there was evidence of posterior right ventricular wall infarction. However, in case 5, there was evidence of stenosis of the re-implanted left main coronary artery both at TEE and autopsy with extensive anterolateral wall infarction of the left ventricle.

Doppler flow characteristics (Table 3)

Color Doppler flow turbulence was present in all but four cases where there were complete obstruction

of the proximal coronary artery (cases 8, 9, 14 and 15). In these four cases there were no demonstrable color flow observed.

Three patterns of spectral Doppler flow were observed.

- Absence of Doppler flow with complete obstruction and an increased velocity in the contralateral coronary artery.
- Severe obstruction with a biphasic high velocity signal > 80 cm/sec both in systole and diastole. In this setting the systolic and diastolic waves did not reach the baseline.
- A diastolic flow velocity between 50-80 cm/sec in conjunction with a short period of systolic reversal of flow.

Myocardial wall motion abnormalities were observed in all patients.

DISCUSSION

Complications related to coronary artery transfer or coronary ostial stenoses remain an important residual cause of early mortality in the pediatric population. Detection of these complications is an important step to

prevent early mortality. Intraoperative transesophageal echocardiography appears to provide the surgeon with an important tool to evaluate the proximal coronary artery connections.

Utilizing TEE, it is possible to image the proximal left and right coronary arteries and detect stenosis, with Doppler confirmation of the findings. This combination strongly supported the conclusion that high velocities arose as a result of partial obstruction within these proximal segments. The association between an increased Doppler velocity within the coronary artery and abnormal segmental wall motion within that territory strongly suggests compromise of coronary blood flow^[8]. Additionally, analysis of the coronary Doppler spectral velocity patterns was helpful in defining coronary artery obstruction. The normal Doppler values for proximal coronary artery flow have been well documented in children by transthoracic echocardiograph^[9-11] and by transthoracic and transesophageal echocardiography in adults^[12-14]. In general a normal pattern is one with a flow velocity not exceeding 50 cm/sec, with a dominant diastolic pattern. It is important to remember that a Doppler angle as close to 0 degrees as possible is important for the velocity data to be valid. An abnormal flow pattern appears to be one with either biphasic high velocity flow of more than 50 cm/sec, an increase in the systolic phase compared to that in diastole or the presence of systolic flow reversal. Techniques to enhance the detection of proximal coronary artery stenosis by echocardiography have utilized either signal enhancement with contrast agents^[15,16] or improved imaging with three dimensional echocardiography^[17].

It is our opinion that transesophageal evaluation of the coronary artery anatomy and flow should be performed intraoperatively in pediatric patients who are at risk for stenosis. As in our population these include cases that have undergone coronary artery re-implantation for an arterial switch operation a Ross procedure or anomalous origin of either coronary artery. Other groups where coronary artery obstruction may be seen are cases with tetralogy of Fallot with conduit insertion or supra-aortic valve stenosis. If at the end of the surgical procedure there is evidence of stenosis of one of the proximal coronary arteries then an assessment of regional myocardial function is important. If this is abnormal it indicates severe stenosis, however the presence of normal segmental wall motion at rest does not exclude an important obstruction. If there are findings of stenosis it is important for the surgeon to review the proximal coronary artery with the abnormal flow to determine if further intervention is necessary.

Specific coronary artery lesions

Isolation of the coronary artery by a deformed

coronary cusp is a rare congenital deformity^[2,4-6]. Thus far cases have been diagnosed by cardiac catheterization or at the time of surgery. The few reported pediatric cases have presented with symptoms of myocardial ischemia and aortic insufficiency. Yoshida *et al*^[4] reported an 11 year-old girl where the left coronary sinus was covered with membranous tissue such that the left coronary ostium could not be identified. This child underwent aortic valve replacement with the internal thoracic artery being used to repair the left coronary artery. Others have reported a membrane-like structure that covered the left sinus of Valsalva almost isolating the ostium of the left coronary artery or severe stenosis of the proximal left coronary and a hypoplastic left aortic cusp^[3]. On initial evaluation our case was felt to represent isolated congenital aortic regurgitation, however detailed assessment of the left aortic sinus and coronary artery demonstrated the trapping of the ostium and the abnormal retrograde flow pattern.

Although most cases who undergo an arterial switch procedure have a relatively uncomplicated course, there are certain subgroups such as those with a single coronary artery or an intramural segment who continue to be at a higher risk for stenosis^[18-22]. In these cases kinking of the single coronary artery or stenosis of the baffle used in a Takeuchi procedure increases the risk of ischemia. In cases with a normal coronary artery pattern the need for routine intraoperative evaluation of the re-implanted coronary arteries is open to debate. However if the routine practice is to perform an intraoperative transesophageal echocardiogram following the arterial switch procedure to evaluate the function and great arterial anastomosis, then assessment of the coronary artery anastomosis should be included.

Other patient groups such as those with supra-avalvular aortic stenosis do appear to be at a higher risk for coronary obstruction^[23-25]. In these cases the ostia of the coronary arteries are often involved in the supra-aortic stenosis, with evidence of progressive obstruction as the lesion progresses. With time the distal coronary arteries also become abnormal with the typical corkscrew appearance. The significance of this is supported by data that there is at least a 3% incidence of sudden death in patients with Williams syndrome when followed over a period of 30 years^[26].

We have encountered three cases of Shone's complex, two of who had a single coronary artery pattern. One patient received cardiac transplantation for left ventricular failure. We were only able to demonstrate a systolic reversal flow pattern in the left coronary artery system, which we explained as coronary artery spasm. This, however, was shown at autopsy to be a fibrointimal proliferation of the internal elastica. The two other patients had a Ross-

Konno procedure, which was complicated by a right coronary artery stenosis, one of whom deceased in the immediate postoperative period due to severe biventricular failure.

Complications related to coronary artery re-implantation are an important cause of early mortality after the Ross-Konno procedure^[27-29]. In our study, we encountered five such cases. In three, the right coronary artery was involved, in the fourth, both the left main and right, while in the fifth, there was kinking of the left coronary artery that was of questionable significance. This surgical procedure may result in ostial damage from retraction of the aorta, narrowing or distortion of the ostia due to misplacement of distal suture line, air or particulate matter resulting in embolization or in the case of root replacement, kinking during re-implantation of the coronary arteries. Our current policy has been to perform an angiogram in all cases that have had previous surgical procedures and preoperative transesophageal echocardiogram in all cases. Our current opinion is that following completion of the surgical procedure, both coronary arteries should be evaluated and that, if a stenotic pattern is identified, then consideration should be given to further intervention.

The prompt and complete detection of complications that may occur after first-stage palliation for hypoplastic left heart syndrome is important. Such complications may be life threatening or limit the suitability of the infant for a staged bi-directional Glenn anastomosis. Meliones *et al*^[30] in a longitudinal study reported the complications encountered after first-stage palliation. They reported tricuspid valve regurgitation (13%), ventricular dysfunction (29%), and neo-aortic regurgitation (13%), and 58% of all deaths occurred within the first 24 hours due to cardiovascular collapse. Bartram *et al*^[31] studied 122 autopsy specimens following postmortem, and reported that an important cause of death was impaired coronary perfusion (27%) due to pre-coronary obstruction (i.e., the native aortic root). They emphasized fatal complications after Norwood's procedure were largely due to technical and surgically correctable lesions. Although uncommon, our case was left main coronary artery occlusion rather than pre-coronary obstruction.

It is uncommon to develop signs of myocardial ischemia following insertion of an extracardiac conduit. If this is encountered, the mechanism is usually coronary artery compression by the conduit, in particular, the right coronary artery. The reported incidence is 0.35^[1]. In our series, we encountered only one patient with complex congenital heart who had coronary artery compromise following insertion of a right ventricle to pulmonary artery conduit. Intraoperative TEE demonstrated evidence of a segmental wall motion abnormality in the territory of

right coronary artery. At the time the significance of the lack of flow in the right coronary artery was not fully appreciated until a subsequent cardiac catheterization demonstrated proximal right coronary artery stenosis which was dealt with by stenting the vessel.

Although some of the findings appear obvious in retrospect, early on in our experience we were unsure as whether some of the findings represented poor imaging, as in the cases of absent flow or coronary spasm in those with an increased velocity. By evaluating the cases in detail, plus having confirmation of the echocardiographic findings we are now more confident in our interpretation of the intraoperative or postoperative transesophageal echocardiographic results.

Coronary artery flow:

The increase in coronary blood flow is regulated by changes in diameter, and consequently the vascular resistance of the coronary arteries. The major epicardial coronary arteries and their principal branches serve as conductance vessels and, in the absence of coronary artery disease, contribute only about 5% to total coronary vascular resistance. In contrast, intramyocardial coronary arterioles are responsible for the majority of coronary vascular resistance. The normal pattern of phasic coronary artery flow velocity is characterized by a small forward flow during systole (S wave) and a large forward flow during diastole (D wave). Cardiac contraction affects coronary blood flow resulting in this phasic coronary arterial flow. During cardiac contraction coronary arterial flow is small, and in diastole coronary arterial blood flow is large. When there is a complete obstruction in one coronary artery, there is a compensatory increase in the flow of the other coronary artery. However, when there is a partial obstruction in one coronary artery, there is increase in both systolic and diastolic flow phases of the coronary flow. The possible mechanism of systolic reversal flow in four of our patients could be either due to coronary artery spasm or hypertrophied left ventricle. In the latter case, the systolic intramyocardial pressure and the intramural peri-vascular pressure may be so high in the hypertrophied left ventricular wall that the coronary artery resistance increases during systole resulting in backward flow.

The first two patterns (a and b) are highly suggestive of coronary artery stenosis, however, the last pattern (c) should be looked at in the context of other parameters like wall motion abnormalities and a decrease in left or right ventricular ejection fraction.

Limitations

Many physiologic conditions may influence coronary flow and velocity profiles. Conditions such as tachycardia or bradycardia and states that increase

wall stress^[32] have an impact on the Doppler profile. Also, various pharmacological manipulations in the intraoperative period affect coronary flow and thus Doppler profiles. Furthermore, the coronary arteries move continuously in and out of the imaging plane in concert with the normal cardiac cycle. Therefore, for any given cardiac cycle, the coronary arteries are probably in view less than third of the time. Thus the examiner has to locate those few frames in which the coronary arteries are visible. Yoshida and associates^[8] demonstrated that only the proximal coronary artery pathology could be demonstrated, as echocardiographic imaging is tomographic by nature and the epicardial vessels follow the curved surface of the heart.

A large angle of incidence to the Doppler beam will also result in underestimation of the Doppler velocity. Fortunately the right coronary artery lends itself to parallel imaging, with similar findings in the left anterior descending and circumflex coronary arteries. The left main coronary artery can be a problem; however with multiplane imaging it is usually possible to overcome this limitation.

CONCLUSION

TEE imaging and Doppler interrogation of the proximal CA's reliably detects stenoses and may provide important information leading to surgical revision of the CA anastomoses. We suggest routine perioperative TEE assessment of proximal CA anastomoses following surgical reimplantation.

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Original Article

Short and Long Term Outcomes of Repaired Complete Atrioventricular Septal Defects: Risk Factor Analysis

Amira Ahmad Abdulla Hay Al-Hay¹, Lulu Abushaban¹, Ali Al-Hassan¹, Muath Alanbaei², Velimir Stojanovic³

¹Department of Pediatric Cardiology, Chest Diseases Hospital, Kuwait

²Adult Congenital Heart Diseases Unit, Chest Diseases Hospital, Kuwait

³Department of Cardiac Surgery, Chest Diseases Hospital, Kuwait

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ABSTRACT

Objective: To study rates of survival and incidence of reoperation of complete atrioventricular septal defects (CAVSD) repair in Kuwait and to determine the risk factors affecting surgical outcome

Design: Retrospective study

Setting: Chest Diseases Hospital, Kuwait

Subjects: One hundred and forty consecutive patients during the 16-year period between January 1992 and December 2007

Intervention: Surgical correction for CAVSD

Main Outcome Measures: Short and long-term surgical outcomes of repaired CAVSD; demographic, cardiac and surgical risk factors that influence the postoperative mortality and morbidity

Results: Median age and weight at primary repair were 4.4 months and 5 kg respectively. Down syndrome was diagnosed in 78.6% of the patients. The operative mortality was 12.9%

(95% CI 7.5, 18.3). Significant postoperative complications, relative hypoplasia of left atrioventricular valve (LAVV) and / or left ventricle were shown to be independent risk factors of operative mortality in multivariate Cox's model ($p < 0.01$). Actuarial estimate of survival at six months and 15.5 years following definitive repair after discharge was 99.1% and 98%, respectively. Freedom from reoperation at 16.5 years after definitive operation was 93.5% (95 % CI 89.4, 97.6); most reoperations were related to LAVV regurgitation. In the multivariate model with LAVV dysplasia (2/8 = 25%) and hypoplasia (2/7 = 28.6%), patients with such valve abnormalities had less freedom from reoperation ($p < 0.001$). **Conclusions:** Left heart obstructive lesion was shown to be an independent risk factor for CAVSD surgical outcomes. Detailed evaluation for such lesions should be performed peri-operatively to reduce the impact on operative mortality and LAVV reoperation.

KEY WORDS: atrioventricular canal defect (AVCD), Down syndrome (DS), pulmonary artery banding (PAB), tetralogy of Fallot (TOF)

INTRODUCTION

Chest Diseases Hospital is the main solitary Tertiary Cardiac Center in Kuwait that takes care of all patients with congenital heart diseases (CHD). Almost all Down syndrome (DS) patients are referred to Chest Diseases Hospital for screening to rule out CHD. There are two major well-defined categories in atrioventricular septal defect (AVSD). In ostium primum atrial septal defect, or partial atrioventricular septal defect, the left and right atrioventricular valves (AVV) guard a common atrioventricular junction with only interatrial communication^[1]. In complete AVSD (CAVSD), common AVV with five floating leaflets guards the common atrioventricular junction^[1]. In addition, there is an interatrial and a large interventricular communication. Patients with restriction of the interventricular communication with common or

divided AVV are classified as an intermediate group of AVSD^[1]. Results of surgical correction for patients with CAVSD have been improving universally over the last two decades; however, left atrioventricular valve (LAVV) dysfunction before and after correction has remained a major factor in predicting operative death and the risk of reoperation^[2-4]. Although the surgical outcome of CAVSD is well reported internationally^[2-4], morbidity or mortality are not known from Kuwait after 1996^[5]. It is well known that primary repair is superior to initial palliation in children with CAVSD although it is unavoidable in specific situations^[4]. The purpose of this study was to evaluate surgical outcomes of early and late survival rates in patients diagnosed to have CAVSD during the 16-year period (1992-2007) and to identify risk factors for operative mortality and reoperation.

Address correspondence to:

Amira Ahmad Abdulla Hay Al-Hay, MRCPped (UK), Consultant Pediatric and Fetal Cardiologist, Chest Diseases Hospital, Kuwait.
PO Box 4278 Salmiya, ZIP Code: 22043. State of Kuwait, Telefax: 00965-24829613. E-mail: amira_alhay@hotmail.com

SUBJECTS AND METHODS

Retrospective evaluation of medical records of 228 patients with CAVSD between January 1992 and December 2007 at the Chest Diseases Hospital in Kuwait was done. Both partial and intermediate types AVSD were excluded from this study. One hundred and forty patients (61.4%) who underwent complete repair were included. The remaining 88 cases were excluded because 13 (14.8 %) died before repair or after palliation, 12 (13.6%) were inoperable, 11 (12.5%) were lost to follow-up and 52 patients (59.1%) with atrial appendages isomerism or biventricular repair were not considered feasible. Out of all the CAVSD patients, 93.6% presented with heart failure and / or failure to thrive, while 6.4% had additional tetralogy of Fallot (TOF) and presented with cyanosis. DS was present in 110 (78.6%) patients. Cross-sectional echocardiography evaluation was done to confirm the diagnosis of CAVSD, the degree of left and right AVV regurgitation and the presence of additional anomalies. Cardiac catheterization and angiography was performed in 60 (42.9%) patients prior to surgical repair.

Operative death was defined as early death after repair while the patient was in the hospital or within 30 days of surgery. Reoperation was defined as a second operation that required cardiopulmonary bypass. Follow-up information in all patients was obtained until June 30, 2008.

This study was approved by the local ethical committee.

Operative Technique:

Repair was carried out using a standard cardiopulmonary bypass technique with moderate or profound hypothermia (median 26 °C, range 15 to 35 °C). Deep hypothermic circulatory arrest was used in 15 patients who were under three months. All had cold crystalloid cardioplegia solution. The median cardiopulmonary bypass (CPB) time was 60 minutes (range 25 to 229 min). The median cross-clamp time was 55 minutes (range 29 to 145 min). Two patches repair were performed for all patients. Autologous pericardial patches were used for atrial defect component while for ventricular defects Gortex patches were used in 74 (52.9%), Dacron in 45 (32.1%) and xenotic pericardial patches in 21 (15%). Sutures were placed in the septal commissure (line of apposition between left superior and inferior bridging leaflets) in 120 patients (85.7%) using pericardial pledget stitches. Partial stitching (43.3%) was defined as the use three or lesser stitches and complete stitching for repairing LAVV was defined as the use of four stitches or more (56.7%). Commissuroplasty of LAVV was performed in five patients to reduce the LAVV incompetence.

Statistical methods:

Surgical outcomes with 95% confidence intervals (CI) were calculated using the technique described by Altman^[6]. Univariate analyses were used to assess whether there was a relationship between surgical outcomes (operative mortality or reoperation) and possible predictors. These predictors were demographic (age, weight at operation, sex, presence of DS and year of operation), cardiac (presence of heart failure, degree of LAVV regurgitation, relative hypoplasia of LAVV, double orifice LAVV, dysplastic LAVV, presence of single papillary muscle (PM) of LAVV, relative hypoplasia of right or left ventricles (LV) and presence of additional cardiac anomalies), and surgical variables (type of patch used to close the interventricular communications, whether or not septal commissure of LAVV sutured, cardiopulmonary bypass time, aortic cross-clamp time, time on mechanical ventilator, inpatient period and postoperative complications). To agree on the term of relative hypoplasia of the LV retrieved from preoperative transthoracic echocardiogram (TTE) reports that were obtained from patient's medical record and preoperative TTE tapes were reviewed by an independent blinded observer. The patients were approved to have a relative left or right ventricular hypoplasia, yet considered for biventricular repair, only when both ventricle end diastolic length ratio ranged between 70 to 80% from each other. These measurements were performed by a blind observer and compared to old TTE reports for only suspected patients reported to have these abnormalities in cardiac dimensions and / or valves. The observer measured each ventricular length starting from the mid-AVV to the apical endocardial layer at end diastole from four-chamber echocardiographic views. Out of seven cases of relative LV hypoplasia in echocardiographic old reports, only six (85.7%) matched. The unmatched cases which were considered normal LV by the independent observer were underestimated because of severe tightness of the band which resulted in right ventricular dilatation and compression of the LV cavity. They were considered as normal LV dimension in statistical analysis. Relative left or right AVV hypoplasia was defined on the basis of echocardiographic measurement expressed as a ratio when one of the valve areas was less than 75% and more than 50% of the other. This was approved and matched the old reporting by the independent observer in all suspected patients. An atrial fenestration was created in 33.3% of relative LV hypoplasia patients to improve the physiologic tolerance to biventricular repair in selected patients. Fisher's exact test was used for categorical data. Univariate hazard ratios and their 95% CI were estimated for variables

Table 1: Demographic criteria of repaired CAVSD

Group	n	Age (months) median (range)	Weight (kg) median (range)	Sex (F) n (%)	Kt n (%)	DS n (%)
CAVSD	140	5.6 (1.7- 53)	4.5 (2.7- 16.8)	86 (61.4)	96 (68.6)	110 (78.6)
Primary repair	113	5.1 (1.7- 15.1)	4.4 (2.7- 8)	76 (88.4)	83 (86.5)	94 (85.5)
TOF	9	15.7 (6- 40.4)	9.3 (3.3- 10)	4 (4.7)	7 (7.3)	9 (8.2)
Deband PA & repair	18	11.2 (7.7- 53)	10 (2.7- 16.8)	6 (7)	6 (6.3)	7 (6.4)

F = female, Kt = Kuwaiti, DS = Down syndrome, TOF = tetralogy of Fallot, PA = pulmonary artery

found to have a statistically significant ($p < 0.05$) relationship with surgical outcome. Multivariate forward stepwise logistic regression model was performed to assess the impact of selected variables on events (hospital death, reoperation) controlling for potential confounders. The results quoted are for the hazard ratio with 95% CI. Kaplan-Meier actuarial survival curves and log-rank test were calculated for

Table 2: Clinical and echocardiographic characteristics of the CAVSD patients in Kuwait (1992-2007)

Anomalies	n (%)
Left AVV regurgitation	
Absent	42 (30)
Mild	68 (48.6)
Moderate	27 (14.3)
Severe	3 (2.1)
Associated Left AVV abnormalities	
Dysplasia	10 (7.1)
Relative hypoplasia	8 (5.7)
Single papillary muscle	7 (5)
Double orifice	3 (2.1)
Additional anomalies	
Persistent arterial duct	40 (23.6)
Ostium secundum atrial septal defect	33 (23.6)
*Relative ventricular hypoplasia (6 left, 10 right ventricles)	16 (11.4)
Additional tetralogy of Fallot	9 (6.4)
Double outlet right ventricle	5 (3.6)
Common atrium	3 (2.1)
Coarctation of the aorta	2 (1.7)
Subvalvar aortic stenosis (mild)	1 (0.7)
Left SCV to coronary sinus	1 (0.7)

AVV = atrioventricular valve, SVC superior caval vein, *Relative ventricular hypoplasia ; All these anomalies were confirmed during surgery.

hospital and overall mortality and for freedom from reoperation. All statistical analyses were conducted using the software package of social science (SPSS, version 9).

RESULTS

One hundred and thirteen patients underwent primary repair at a median age of 5.1 months. However, 23 (16.4%) required early palliative procedures of which 18 (78.3%) underwent pulmonary artery banding (PAB) (2 with additional ligation of Patent Ductus

Arteriosus, PDA), three (13%) underwent unilateral modified Blalock-Taussig shunts, and two (8.7%) had coarctation of the aorta repair and PDA ligation. Demographic data of CAVSD subgroups are presented in Table 1. Out of the first primary repaired subgroup (113 patients), 19 (16.8%) were operated upon in the first three months of life, 80 (70.8%) in the first six months and 108 (95.6%) in the first year. The second subgroup was CAVSD-PAB patients (18), of which four (22.2%) were operated on within the first year and the remaining were operated upon in two years. Out of the nine patients (3rd subgroup) with CAVSD and additional TOF, six (66.6%) were operated upon in the first year of life and the remaining in the second year. The clinical and echocardiographic characteristics of left and right AVV and presence of additional cardiac lesions are presented in Table 2.

Hospital mortality:

Among the 140 patients considered in this study, 18 (12.9 %, 95% CI 7.5, 18.3) died in early post-operative period. A Chi-Square test showed that there was no difference in hospital death of patients undergoing primary repair of CAVSD in relation to the three CAVSD subgroups, namely primary repair, deband and repair, and CAVSD plus TOF ($p = 0.87$) as was the survival analysis of these subgroup (log-rank test $p = 0.9$). The hospital death cases are described in Table 3. The main cause of operative death was low cardiac output state (61.1%) while hypertensive crisis occurred in 16.7%. None of CAVSD patients with normal chromosomes died after primary repair.

Demographic variables:

There was no significant difference in operative weight and age between those who died in CAVSD primary repair group (median weight = 4.6 kg and age = 8.5 months) and those who survived (median weight = 5.1 kg and age = 6.6 months, $p = 0.09$ and 0.76 respectively). Operative mortality rates were examined according to whether the operation occurred before 1998, 7/61(11.4%) or after, 11/79 (13.9%) and there was no significant difference ($p = 0.81$). The operative mortality for children with DS, 18/110 (16.4%) was significantly higher from that of chromosomally

Table 3: Operative mortality cases after repair of CAVSD*

Case No.	Age (month)	Sex subtype	CAVSD repair	Year at repair	Associated lesion	Main cause of death	Other causes
1	36.2	F	PR	1993	1PM, parach, LAVV&LV hypopl	LOS	PHT, LV dysfunction
2	6.1	F	PR	1994	LAVV hypopl & prolapse	LOS	LV hematoma
3	2.4	M	PR	1997	1PM, LAVV hypopl, PDA	LOS	
4	10.9	M	dePAB	1998	-	LOS	
5	16.1	F	PR	1999	-	LOS	PHT crisis
6	5.6	M	PR	2000	ASD2	LOS	PHT crisis
7	15.8	M	de PAB	2001	RAVV& RV hypopl	LOS	SVT
8	4.1	M	PR	2002	ASD2, LV hypopl	LOS	SVT, septicemia
9	6.0	F	PR	2002	1PM, parach	LOS	moderate+ LAVV stenosis
10	6.3	F	PR	2003	PDA	LOS	
11	3.3	M	PR	2005	LAVV hypopl	LOS	
12	10.1	M	PR	1995	PDA		PHT crisis
13	3.5	M	PR	1996	PDA		PHT crisis LOS
14	5.2	M	PR	2001	ASD		PHT crisis
16	3.5	M	PR	2002	1PM, LAVV & LV hypopl	can't wean off CPB	
17	3.0	F	PR	2006	ASD, PDA	can't wean off CPB	
18**	2.5	F	TOF	1998	TOF	Septicemia, DIC	Fungemia

* All operative mortality cases had Trisomy 21; **This patient required LAVV reoperation after primary repair and died after reoperation. CAVSD=complete atrioventricular septal defect, F=female, PR=primary repair group, 1PM= single papillary muscle, parach=parachute valve, LAVV=left atrioventricular valve, LV=left ventricle, hypopl=relative hypoplasia, LOS=low output state, PHT=pulmonary hypertension, M=male, PDA=persistent arterial duct, dePAB= pulmonary artery banding and CAVSD repair, ASD2=ostium secundum atrial septal defect, RAVV=right atrioventricular valve, RV= right ventricle, SVT=supraventricular tachycardia, CPB=cardiopulmonary bypass, TOF =additional tetralogy of Fallot group, DIC=disseminated intravascular coagulation.

normal children (0/30 = 0%, p = 0.01, Odds ratio = 1.2, 95% CI 1.1, 1.3). Freedom from CAVSD operative mortality of the chromosomal normal children was 100% compared to 83.1% of DS patients which showed statistical significance (log-rank test p = 0.02, Fig. 1).

Cardiac variables:

The following were not significantly associated with a risk of operative death: degrees of pre-operative LAVV regurgitation (p = 0.2), the presence of other cardiac anomalies such as an ostium secundum atrial septal defect or PDA or other anomalies (p > 0.05). In a univariate analysis (Cox regression test), among eight patients with relative hypoplasia of LAVV, there were five operative deaths (p < 0.001, Hazard

ratio = 11.5, 95% CI 3, 45). Two further important risk factors for early death were the presence of a relative hypoplastic LV (3/6 = 50%, p = 0.01, Hazard ratio = 7.6, 95% CI 1.6, 35.7), and a single PM of LAVV (3/7 = 42.9%, p < 0.02, Hazard ratio = 6.4, 95% CI 1.3, 30.1). New variable was formed by collapsing the three significant left-sided structural lesions, namely single PM of LAVV, relative hypoplasia of LV and LAVV. Cumulative survival of operative mortality studied in a Kaplan-Meier survival analyses against left sided lesion variable showed that those with left structural abnormalities were significantly at a higher risk for operative mortality (Log rank-Test p<0.01, Fig. 2, p < 0.01, Hazards Ratio = 6.1, 95% CI 1.7, 21.5). To analyze the impact of other LAVV abnormalities on relatively

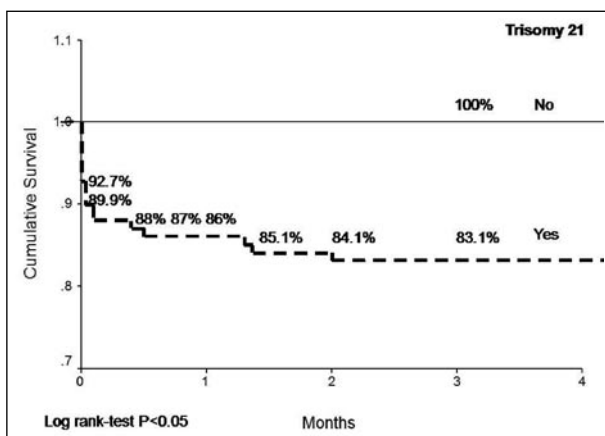


Fig. 1: Survival analysis after CAVSD repair showing significant difference in survival function between the Down and non-Down patients (log rank test p < 0.05)

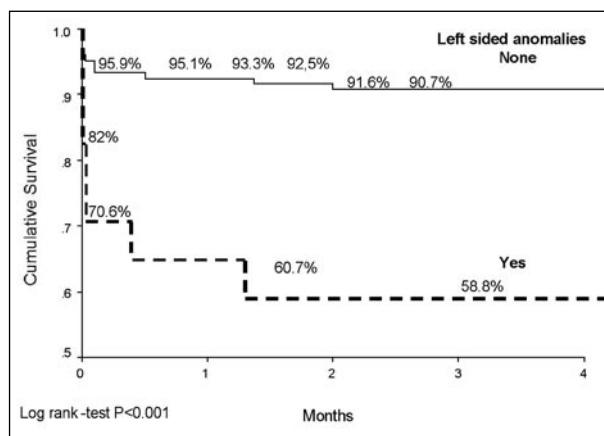


Fig. 2: Survival analysis post CAVSD repair showing that there was statistically significant difference in survival functions between the presence or absence of one or more left sided lesion (log rank test p < 0.001)

hypoplastic LAVV, the hazard ratio of operative death was estimated controlling for whether the LAVV was dysplastic or double orifice or had single papillary muscle or presence of DS. Hypoplastic LAVV was almost 14.1 times at higher risk of operative mortality than for those without ($p < 0.001$, Hazard Ratio = 14.1, 95% CI 14.1, 61.1). However, presence of DS, dysplastic, double orifice valve and single PM of LAVV proved to be insignificant factors.

Surgical variables:

The type of ventricular patch and the placement of sutures across septal commissure were not found to be statistically significant ($p = 0.9$ and $p = 0.19$ respectively). In patients who died early, the median CPB time and aortic cross clamp time were longer (90, 62 minutes), than the median in survivors (58, 50 minutes), but this did not reach statistical significance except in CPB time ($p < 0.01$, $p = 0.23$ respectively). Time of ventilation in hospital showed no significance in operative mortality.

Postoperative Complications:

Overall complications occurred in 36 patients (25.7%). Low cardiac output state (LOS) was diagnosed in 12 (8.6%) patients and pulmonary hypertensive (PHT) crisis in nine cases (6.4%). Effusions that required drainage were three pleural effusions, three pericardial effusions and one chylothorax. Four patients developed septicemia, one patient developed LV hematoma. Four patients required permanent pacemaker for complete heart block and three developed supraventricular tachycardia, which required antiarrhythmic medications. A new variable was created by collapsing the three significant postoperative complications risk factors namely PHT crisis, LOS and sepsis. This was tested as a surgical risk factor for operative mortality. The development of such complications postoperatively turned out to be a highly significant risk factor for in-hospital mortality ($p < 0.001$, Hazards Ratio = 10.3, 95% CI 2.9, 35.8). These important risk factors for hospital death LOS and PHT crisis occurred genuinely in patients with DS.

A multivariate Cox's regression analysis was performed to establish the predictors for operative death in all the statistically significant risk factors LAVV hypoplasia, LV hypoplasia and postoperative complications remained significant independent risk factors when controlled for others ($p < 0.01$, Hazard Ratios = 6.7, 13 and 13 respectively).

Overall mortality:

Out of all survivors, two (1.6%) patients died later after discharge from hospital. The first died 6.5 months post repair from severe septicemia. The latter died 17.5

months post repair and was brought dead. Although reason was not obvious, arrhythmia was suspected. Actuarial survival six months and 15.5 years after discharge was 99.1% and 98% respectively. In contrast with early mortality, there were no significant risk factors for late death.

Reoperation:

Out of the 140 children included in this study, 138 survived corrective surgery and were considered available for reoperation. All analyses of risk factors for reoperation are thus limited to this group. Out of these 138, nine patients (6.5%, 95% CI 2.4, 10.6) required reoperation (6 for LAVV regurgitation, 1 for residual atrial septal defect, 1 for residual ventricular septal defect and 1 for enlargement of obstruction of superior caval vein with a Gortex patch). Median time for reoperation was 1.3 months (range: 0.1- 77.7 months). Of the nine patients, three (33.3%) were re-operated in the first month post repair, six in the first year and eight in the first three years. Of these one died within 60 days from the initial operation and was already included in the operative mortality analysis (Table 3, patient number 18). The survival function from reoperation for CAVSD subgroups were not significantly different (Log rank-test $p = 0.72$). Out of the six repaired LAVV, one required replacement with size 23 mm HP Saint Jude medical prosthesis and one required LAVV repair on two occasions.

Age at operation, weight, presence of DS and year of operation (≤ 1998 , ≥ 1999) showed no significant correlation with the need for reoperation ($p = 0.69$, $p = 0.3$, $p = 0.12$ and $p = 0.09$ respectively). Freedom from reoperation was not affected by the degree of pre-operative LAVV regurgitation and the trend was not significant ($p = 0.14$). To satisfy the proportional hazards criteria when estimating the univariate hazard ratio, the data was collapsed to two levels (no or mild regurgitation Vs moderate to severe regurgitation) and the resultant measure of risk was again statistically insignificant ($p = 0.61$).

Children with a dysplastic LAVV were found to have a higher rate of reoperation (33.3% with Vs 4.5% without dysplasia; $p = 0.01$, Odds ratio = 10.5, 95% CI 1.6, 69.1). Another cardiac variable that was significantly associated with LAVV reoperation was the hypoplastic LAVV ($p < 0.01$, Odds ratio = 12.7, 95% CI 1.9, 86.5). Patients with LAVV dysplasia or hypoplasia were found to have a significantly lower probability of freedom from LAVV reoperation than those without these abnormalities (Log rank-test $p < 0.001$, Fig. 3). Additional anomalies such as PDA, common atrium, relative hypoplasia of the LV and other anomalies were not found to be statistically associated with the need for LAVV reoperation ($p = 0.73$, $p = 0.34$, $p = 0.12$ and $p = 0.13$ respectively). All tested surgical variable (CPB

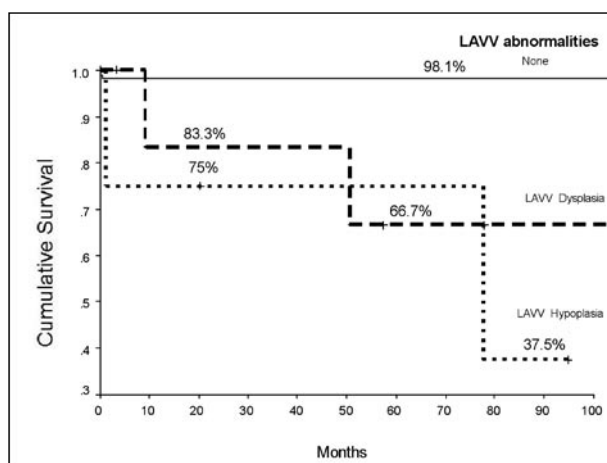


Fig. 3: Analysis of the time to reoperation for all patients stratified by the absence or presence of dysplastic and hypoplastic LAVV. There was significant difference in survival functions between the three groups (log rank test $p < 0.001$) and patients with a dysplastic and / or hypoplastic LAVV had lower probability of survival (in terms of freedom from reoperation).

time, aortic cross clamp time, patch type and LAVV stitch) were found insignificant in relation to freedom from reoperation ($p = 0.82$, $p = 0.47$, $p = 0.46$ and $p = 0.55$ respectively).

A multivariate Cox's regression model including age at repair, DS, LAVV dysplasia and LAVV hypoplasia was generated. This showed that when controlling for DS and age at operation, the p-value of the hazard of LAVV reoperation for patients with LAVV dysplasia and hypoplasia continued to be statistically significant ($p = 0.04$, hazard ratio: 9.0, 95% CI 1.11, 80 and $p = 0.01$, hazard ratio: 12.1, 95% CI 12.1, 90, respectively).

Follow up:

The follow-up of survivors was complete in 96.7% (118/122). The mean (median) follow up time after hospital discharge was 4.3 (3.9) years (range 0.27 to 15.2 years). Out of all preoperative mild and less LAVV regurgitation, 98 (83.1%) survived postoperatively and only nine (9.2%) progressed to moderate and four (4.1%) to severe LAVV regurgitation. Out of 20 (16.9%) patients with preoperative moderate plus LAVV regurgitation, 14 (70%) patients improved to less than mild, four (20%) continued to be moderate and two (10%) had severe regurgitation. In six patients who underwent LAVV reoperation, four improved to mild or less of LAVV regurgitation and only one continues to have moderate incompetence which is controlled by medication. Mild LAVV stenosis was present in three patients who were asymptomatic. Eleven patients had a hemodynamically insignificant small residual ventricular septal defect at one year follow up that closed spontaneously. The clinical findings were confirmed by cross-sectional echocardiography.

DISCUSSION

Operative mortality at definitive operation was within the range of other studies (12.9%)^[7-13]. In several studies as in our series, pulmonary artery banding, as a palliative procedure in early infancy was not recommended unless other associated abnormalities would have made primary repair a high-risk operation^[9,10,14,15]. One or two stage repair was not a significant risk factor for operative mortality in our series^[16].

Clapp and colleagues^[17] in 1990 showed that children with CAVSD and DS developed early pulmonary vascular disease in the first year more frequently than children with normal chromosomes. Early repair of CAVSD especially in Trisomy 21 before the patient reaches six months of age to prevent development of pulmonary vascular disease is a well recognized entity^[16,18]. We showed that DS plays a significant role in the surgical outcome of CAVSD with a lower survival rate postoperatively^[10,12]. Out of the 110 operated DS patients, 18 (16.4%) had operative death in comparison to zero in normal chromosome patients ($p = 0.01$). Another series however, showed that CAVSD operative mortality for those with co-existing DS was similar^[16,19] or even lower^[20] than those chromosomally normal. In our series, 38 primary repair cases were operated on at the age of six months and older with six (15.8%) operative mortality in this group of patients but it was statistically insignificant ($p > 0.05$). The rationale for delaying the repair of these CAVSD after six months of age was not documented from medical records. These patients underwent cardiac catheterization to measure the pulmonary vascular resistance and pulmonary arterial pressure. The reversibility of pulmonary vascular resistance and hypertension with 100% oxygen were measured to ensure suitability for CAVSD surgical repair.

In our series, patients with DS and CAVSD had more risk of postoperative complications such as LOS and PHT crisis which were the main causes of death in 14 cases (77.8%). Journois *et al*^[21] showed that in postoperative PHT crisis, nitric oxide (NO) inhalation played an important role in reducing postoperative mortality in children operated for CAVSD. We knew the importance of the proper management of postoperative PHT crisis in reducing early deaths. However, NO was not administered as it was not available in the hospital during the study period. Fortunately, it is now available and its administration will probably have a major impact on decreasing PHT crisis operative mortality.

In contrast to other studies, the degree of LAVV regurgitation^[7,13] and suturing the septal commissure^[7,22] were not risk factors for early death in our series. Redmond *et al*^[15] showed that hospital

mortality was higher in CAVSD patients with relative hypoplasia of LV (20%) which they considered as a complex group than in the normal LV size group (2.3%, $p = 0.004$) that is comparable to the rate in our series. Cohen and others^[23] as in our series, showed that relative right ventricular hypoplasia is better tolerated than LV hypoplasia, and biventricular repair is usually safer. Nashimura and colleagues^[24] postulated in a case report that in PAVSD patients even when the preoperative LV volume is small, if it is reaching the apex, then the LV performance can be expected to be appropriate to tolerate the volume load after repair. In our study, LV to RV end diastole ratio was used to determine the appropriateness for biventricular repair, yet relative LV hypoplasia was an important risk factor for operative mortality.

Preoperative echocardiographic assessment of the adequacy of LV and LAVV can be difficult and whether to send the patient for relative high risk biventricular rather than univentricular repair remains a great challenge for the pediatric cardiologist. Reduction of surgical mortality in such morphology was attempted by performing atrial fenestration (33.3%) to improve the physiologic tolerance to biventricular repair^[25]. In our series, patients with LAVV ratio less than 50% of right AVV were excluded and sent for uni- rather than biventricular repair. However, out of the eight patients with relative LAVV hypoplasia, five (62.5%) could not tolerate the biventricular repair and had early death while three survivors passed the postoperative period smoothly. Out of the three survivors with LAVV hypoplasia and biventricular repair, two required LAVV reoperation and of them one had LAVV replacement with 23 mm Saint Jude prosthetic valve which is consistent with another study^[23].

In our series, the overall actuarial estimate of survival 15.5 years following definitive repair was 98%^[7,12,16,18] which was comparable to other studies. Overall 16.5 year actuarial freedom from reoperation was 93.5% (95% CI 89.4, 97.6)^[11,16]. Most reoperations were related to postoperative LAVV regurgitation (66.7%). Failure of second valve repair led to valve replacement in one out of six patients^[2,8,18,26]. We showed that patients with early age repair were not at higher^[11,27] or lower risk^[12,16] for significant postoperative LAVV regurgitation necessitating LAVV reoperation than those operated at a later age. This was analyzed in patients operated at less than three months of age Vs others operated later (less than six months of age) which showed no difference. Although Pozzi *et al*^[14] and Harkel *et al*^[3] found that preoperative degree of LAVV regurgitation was a significant risk factor for reoperation, unexpectedly we found it was not statistically significant^[7]. Dysplastic^[2,7,16] and hypoplastic^[2] LAVV in our

series and others appear to be major risk factors for postoperative LAVV regurgitation and the need for valve repair or replacement. In contrast with other studies^[11,16,18], our study showed that children with normal chromosomes have the same risk of requiring reoperation as those with DS. After controlling for DS, LAVV dysplasia and hypoplasia remained significant risk factors for LAVV reoperation which is in contrast with others^[16].

Suturing the zone of apposition of the inferior and superior bridging leaflets of LAVV was performed in 85.7% cases. Our series^[7] showed that stitching the zone of apposition of LAVV was not a predictor for freedom from reoperation though it contributed favorably in other studies^[22,26].

Since LAVV abnormality is involved significantly in both surgical outcomes, the assessment of LAVV morphology, whether hypoplastic, dysplastic or even double orifice^[16] should be recognized by preoperative echocardiography, 3D echocardiography and confirmed by transesophageal echocardiography (TEE) perioperatively so that the surgical outcomes regarding freedom from operative mortality or LAVV reoperation could be discussed clearly with parents prior to any surgical intervention. In our series, perioperative TEE has been practiced in the last six years of the study period especially when transthoracic echocardiography suspected some abnormality in the LAVV morphology or TEE was requested by the cardiac surgeon. Yet in our series it did not have any impact on reoperation rate as described by others^[4]. Nonetheless, with increasing learning curve in AVV morphology by TEE, 3D echocardiography and intracardiac echocardiography, an improvement in surgical outcomes in any future study is expected.

Study limitation:

The main limiting factor in this study was that it was a retrospective study and all the data were limited to what was available in patients' medical records. Echocardiographic video tapes of patients diagnosed to have LV or LAVV hypoplasia in medical records were only reviewed to confirm the diagnosis. Tapes were not available for all patients.

CONCLUSION

In conclusion, our series showed that relative hypoplasia of LAVV, relative hypoplasia of LV and postoperative complications were predictors of operative mortality while LAVV hypoplasia and dysplasia were the main predictors for LAVV reoperation. Left sided structure evaluation in patients with CAVSD should be carefully assessed perioperatively and at follow-up to improve surgical outcomes in terms of early mortality and reoperation.

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Original Article

The Possible Association between Tumor Necrosis Factor Alpha C-850T Polymorphism and Childhood Acute Lymphoblastic Leukemia

Fathelrahman Mahdi Hassan¹, Abdelbagi Elnagi Mohamed²

¹Department of Medical Laboratory Science, College of Applied Medical Sciences, Al-Jouf University, Saudia Arabia

²Department of Clinical Microbiology, College of Medical Laboratory Sciences, Sudan University of Science and Technology, Khartoum, Sudan

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ABSTRACT

Objective: To study the possible association between tumor necrosis factor alpha C-850T polymorphism and childhood acute lymphoblastic leukemia (ALL) in Khartoum, Sudan

Design: Prospective analytical case-control

Setting: Medical Laboratory Research Center (MLRC), Khartoum State Teaching Hospital (KSTH), Sudan

Subjects: Sixty-six patients diagnosed with ALL and forty-three apparently healthy adult controls admitted from October 2003 to January 2008

Intervention: Measurement of total white blood cell count, hemoglobin level and genotyping using Sysmex automated analyzer and PCR-amplified

Main Outcome Measure: Analysis of data obtained from the MLRC of the KSTH, Sudan, to determine allele frequency

Results: There was a statistically non-significant decrease in the relative frequency of the TNF α -850T allele detected in the ALL group during the study period ($p = 0.123$). In children with B-ALL a more pronounced but still marginally significant ($p = 0.042$) decrease was found. The odds ratio (OR) for the presence of TNF α -850T allele (CT and TT) was 0.653 (95% CI = 0.327-1.302). The corresponding value for B-ALL, was 0.548 (95% CI = 0.256 -1.174).

Conclusion: The statistically non-significant associations of TNF α - 850T polymorphism suggests the need to investigate the risk for childhood ALL or the presence of fever, anemia, leukocytosis and leukopenia at diagnosis.

KEY WORDS: acute lymphoblastic leukemia, hematological malignancies, leukemia

INTRODUCTION

Tumor necrosis factor alpha (TNF α), a 17 kilo Dalton (KDa) protein (a cleavage product of a 29 KDa membrane-associated protein) encoded by gene stationed on chromosome 6 near the major histocompatibility complex, is capable of functioning as a direct inhibitor of progenitor cell growth^[1].

TNF α is a potent immunomediator and proinflammatory cytokine, implicated in a number of disorders^[1]. As it promotes the growth of lymphoid cells and influences the prognosis and response to therapy of patients with cancer it presents itself as a good candidate for an association with hematologic malignancies and their clinical manifestations^[2]. Higher levels of serum TNF α have been detected, at diagnosis, in children with malignancies, including acute lymphoblastic leukemia (ALL)^[3]. Also, higher levels of TNF α have been associated with febrile episodes at diagnosis in children with acute leukemia^[4]. Polymorphisms in the promoter region

of the TNF α gene are known to affect plasma levels of the cytokine, and TNF α high producing alleles were associated with disease progression on some forms of hematological malignancies^[2] but not in childhood ALL^[5].

The C \rightarrow T substitution at position - 850 (C-850T) gives rise to a polymorphism recently identified in the promoter region of the human TNF α gene^[6,7]. The polymorphism lies very close to two other, previously described polymorphisms, reported to affect the transcriptional activity of the TNF α gene, namely TNF α C-857T and TNF α C-863Q, as opposed to other TNF α promoter region polymorphisms^[1]. To the best of our knowledge, no recent study has examined, so far, the possibility of an association of TNF α C-850T with any type of hematologic malignancy. On the other hand, the fact that TNF α C-850T was shown to affect the risk for vascular dementia in at least one population^[8] argues in favor of a functional significance for this polymorphism.

Address correspondence to:

Dr Fathelrahman M.Hassan, M.Sc, PhD, College of Applied Medical Science, Al-Jouf University, Saudia Arabia. Tel: +966535121591/ +966596256120, E-mail: fathmaga@yahoo.com

Therefore, the main aim of this study was to analyze the distribution of the TNF α C-850T polymorphism in children with ALL, as well as in healthy controls in Khartoum, Sudan, and to examine its possible association with clinical and laboratory findings at diagnosis, such as fever, anemia, leucocytosis and leucopenia.

PATIENTS AND METHODS

This is a prospective analytical case-control based study conducted in Khartoum State Teaching Hospital (KSTH), Sudan during the period from October 2003 to January 2008 to determine the possible association between TNF α C-850T polymorphism and childhood ALL in the Sudanese population.

A total of 66 patients were analyzed. All patients had been diagnosed as having ALL (36 boys, 30 girls). Fifty-two out of these patients (30 boys, 22 girls), had been diagnosed as having B - cells ALL and the rest had pre B - ALL and T- ALL. All patients were under treatment. The study also included 43 apparently healthy adult individuals (20 male, 23 female) as control group. Both patients and controls were less than 15 years of age and were Sudanese nationals.

This study was approved by the local ethical hospital committee.

A structured questionnaire consisting of items including demographic data, family history and laboratory investigations was administered to all patients. An informed consent was obtained before collection of blood samples. Blood sample was drawn using a 20 or 21 G needle with limited occlusion of the arm by a tourniquet. The blood was added to the anticoagulant at a ratio of 2.4 ml of blood to 4.2 mg of EDTA (ethylenediamine tetra-acetic acid) and gently mixed. This sample was used for automated platelet count.

The clinical analysis (including presence or absence of fever) and laboratory analysis (total white blood cells - TWBCs, hemoglobin (Hb) level and genotyping) was done for all patients at the time of diagnosis.

Laboratory Methods

Laboratory analysis was done in all patients and controls by measuring TWBCs, Hb level and genotyping analysis.

TWBCs and Hb level was measured using Sysmex automated analyzer; the genotyping was accomplished essentially briefly in the region of the TNF α promoter containing the C-850T polymorphism, was PCR-amplified, using as primers the oligonucleotides: AAGTCGAGTATGGGGACCC CCGTAA (forward) and CCCAGTGTGTGGCCAT ATCTTCTT (reverse). The amplification conditions were 94 °C for 3 min, followed by 40 cycles of 94 °C for 30s, 68 °C for 30s and 72 °C for 1 min and a final extension step of 73 °C for 10 min. The amplified DNA was then subjected to Hind 11 digestion at 37 °C for 4h, and subsequently electrophoretically separated in a 3.5% agarose gel. Under these conditions, the presence of the C allele is revealed by a 108 bp band, whereas that of the T allele by a 133 bp band.

Statistical analysis

Genotype and allele frequency distributions were compared between cases and controls with the X² test of independence. Odds ratios (OR) were calculated with a 95% confidence interval (CI). The Fisher's exact test was used to examine the association between carriage of the TNF α -850T allele and clinical and laboratory findings at diagnosis.

RESULTS

The observed genotype and allele frequencies for patient and control groups are shown in Table 1. An insignificant ($p = 0.123$) decrease in the relative frequency of the TNF α - 850T allele was detected in the ALL group compared to the control group. When the patient group was limited to those children diagnosed with B - ALL ($n = 52$ out of 66) the effect was more pronounced, but still only marginally significant ($p = 0.042$, and with Yate's correction $p = 0.1$, $p = 0.05$). The calculated OR for developing ALL in the presence of the TNF α - 850T allele (CT and TT genotypes) was 0.653 (95% CI = 0.327-1.302). The corresponding value for B-ALL was OR = 0.548 (95% CI = 0.256-1,174). Stratification according to sex did not affect the results. It seems likely that the TNF α C-850T polymorphism was not directly associated with childhood ALL, and that the observed under-representation of the TT genotype in the case samples was most likely due to a chance event. The distribution of the TNF α -850T allele among ALL

Table 1: Genotype and allele frequencies of the TNF α C-850 polymorphism in ALL children and controls

Group	n	Genotypes, n			pa	Alleles, n		p-value
		CC	CT	TT		C	T	
Control	43	23	17	13		122	52	
Pre-B and T-ALL	14	9	3	2	0.385	90	26	0.123
B-ALL	52	33	16	3	0.171	72	16	0.042

Table 2: Relationship between TNF α – 850T allele carrier status and clinical and laboratory findings at diagnosis, in ALL children

Allele carrier status	Fever		Anemia		leukocytosis		Leucopenia	
	+	-	+	-	+	-	+	-
TNF α –850T +d	9	7	10	4	8	6	3	11
TNF α –850T -e	20	14	15	13	14	20	16	18
Significance F (p-value)	1.000		0.338		0.335		0.119	

Anemia - Hb < 9 g/dl, Leucocytosis - WBC > 14000/mm³, Leucopenia - WBC < 6000/mm³, d - CT and TT genotypes, e - CC genotypes, F - Fisher test

patients, according to fever, anemia, leukocytosis or leucopenia at diagnosis, is shown in Table 2. No significant association ($p = 1.000, 0.338, 0.335$ and 0.119 respectively) has emerged from these comparisons. Limiting the patient group to B-ALL only, did not affect this result.

DISCUSSION

The results of this study did not show any direct effect of the TNF α C-850T polymorphism either on the children acquiring ALL or on the occurrence of particular clinical and laboratory characteristics in the event of a positive diagnosis. However, two points deserve some comment. First, it could be argued that the rather small size of our study group limited the statistical power of this study. However, the relatively high prevalence of the TNF α -850T allele as well as the lack of a statistically significant difference ($p = 0.042$) between the entire ALL group and the B-ALL subgroup support the validity of the results. Second, the choice of the control group was made solely to exclude the possibility that any of these individuals would have developed childhood ALL. Obviously, we could not exclude the presence of other pathologies in which TNF α may be involved. This may represent a source of bias in this study. Finally, it should be taken into consideration that these TNF polymorphisms are found in a region of great polymorphic variation in linkage disequilibrium with the human leucocytes antigen (HLA) genes and with each other. Because of differences in the distribution of HLA alleles, one might expect variation in associations between TNF α polymorphisms and various conditions, in different geographical areas. Dissecting out a primary association with TNF α might not be an easy task. It is worth noting that in a recently conducted study, another polymorphism in the TNF locus (G-308A) was reported to increase the protein levels of TNF. This was shown to influence the relapse in (prednisone poor responders) ALL patients. Even though no other effect was detected in any ALL subgroup^[9] additional studies should be undertaken in order to examine the effect of TNF C-850T in various ALL subgroup, and in different ethnic groups, especially since the frequency of this

particular polymorphism has been shown to differ considerably among Sudanese population^[6, 9-11].

CONCLUSION

The TNF polymorphism were found in a region of great polymorphic variation in linkage disequilibrium with the HLA genes and with each other. Because of differences in the distribution of HLA alleles, one might expect variation in associations between TNF α polymorphisms and ALL, in different geographical areas. Dissecting out a primary association with TNF α might not be an easy task. In conclusion, TNF α –850T polymorphism was not directly associated with childhood ALL, and no statistically significant associations have emerged between this polymorphism and either the childhood ALL or presence of fever, anemia, leukocytosis and leucopenia at diagnosis.

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Original Article

Detection of High Risk Human Papilloma Viruses (HR-HPV) in Endocervical Scrapes from Women with Abnormal Cytology in a Turkish University Hospital

Derya Mutlu¹, Alper Kandiser¹, Tayup Simsek², Elif Pestereli³, Dilara Ogunc¹, Meral Gultekin¹

¹Department of Medical Microbiology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

²Department of Obstetrics and Gynecology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

³Department of Pathology, Faculty of Medicine, Akdeniz University, Antalya, Turkey

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ABSTRACT

Objective: To assess the utility of a commercial PCR based HPV test for evaluating patients before colposcopy and colposcopic biopsy sampling in a Turkish hospital and to compare its efficacy with histology in preventing unnecessary colposcopic biopsy sampling

Design: Case control study

Setting: Akdeniz University, Faculty of Medicine, Antalya, Turkey

Subjects: One hundred and seventy-four women with abnormal Pap smear results (40 with high-grade squamous intraepithelial lesions (HSIL) and 134 with low-grade squamous intraepithelial lesions (LSIL) and 34 women with normal cytologic test results were included

Interventions: Papanicolaou stainings and high risk HPV DNA (HR-HPV DNA) detections were done for all endocervical scrape specimens. Colposcopic evaluation and

endocervical sampling were done for 52 patients.

Main Outcome Measures: Papanicolaou stainings, HR-HPV DNA detections and histologic examination from endocervical samplings were evaluated

Results: Human β -globin was not detected in 40 samples. All of the 13 samples from patients with HR-HPV DNA positivity and HSIL were diagnosed as CIN2+ lesions (100%), whereas 23.2% (4/17) of patients with HR-HPV DNA negativity and HSIL were found to have CIN2+ lesions.

Conclusions: HR-HPV DNA test, which also amplifies a genomic fragment as an internal control, seems to be a good screening tool. Besides the benefit of an early diagnosis of cervical cancer, HR-HPV DNA assay may also lead to a marked decrease in unnecessary invasive cervical samplings.

KEY WORDS: cervical cancer, colposcopy, Pap smear

INTRODUCTION

Cervical cancer is a major cause of death among women. In developing countries it is the most frequent female malignancy and in developed countries it is responsible for 7% of all female cancers^[1]. Infection with human papilloma virus (HPV) is the strongest risk factor for cervical cancer^[2]. There are more than 100 types of HPV^[3]. Almost all cervical cancer cases are caused by persistent infection with about 15 genotypes of HPV^[4]. Important co-factors contributing to the persistency of HPV are co-infections caused by HIV and Chlamydia, parity (having more than three children) and smoking; the role of hormonal contraceptives is not clear^[4].

Screening of cervical disease traditionally relied on the Papanicolaou smear. However, due to the high number of false positives and false negatives,

cytological screening alone can be insufficient to assess cervical neoplasia^[5]. In contrast, identification of HPV infection can be more valuable. Because of the poor performance of serological assays and inability of the use of viral isolations effectively, diagnosis of HPV infection is almost entirely based on molecular methods^[6]. With the use of tests detecting high risk HPV genotypes, which have a very high negative predictive value for cervical cancer, it is possible to increase the screening interval for women found to be negative by both cytology and high risk HPV testing^[7].

Roche amplicor HPV test detects 13 high risk HPV types. Moreover it amplifies the β -globin gene as an internal control which evaluates the presence of PCR inhibitors and checks the adequacy of the sample. In addition, the use of AmpErase (uracil-N-glycosylase

Address correspondence to:

Dr Derya Mutlu, MD, Department of Medical Microbiology, Faculty of Medicine, Akdeniz University, Dumlupinar Blv., Antalya, Turkey 07059.
Tel: +90242 2596405, Fax: +90242 2272535, E-mail address: drderyamutlu@yahoo.com

[UNG]) in the master mix, prevents false positivities arising from amplicons from previous PCR runs.

The purpose of the study was to assess the utility of a commercial PCR based HPV test with an internal control for evaluating patient before colposcopy and colposcopic biopsy sampling in a Turkish university hospital where data regarding HPV is lacking and to compare its efficacy with histology in preventing unnecessary colposcopic biopsy sampling.

SUBJECTS AND METHODS

Study subjects

The study population included 174 women with abnormal cytological screening results, attending Akdeniz University Medical Faculty Hospital Obstetrics and Gynecology department between April 2005 and July 2006. The cytological screening results were reported as low-grade squamous intraepithelial lesion (LSIL) for 134 patients and high-grade squamous intraepithelial lesion (HSIL) for 40 patients according to 2001 Bethesda System terminology^[8]. Additionally 34 patients, whose cytologic screening results were reported as normal, were included in the study as a control group. All participants were informed of the research and their informed consent was taken. The ethics committee of Akdeniz University Hospital reviewed and approved the study. Information related to their tobacco use and live birth number was recorded.

Cytologic and histologic examination: Endocervical scrape specimens were collected from the patients by a gynecologist with cervix brush technique. Specimens were placed in PreservCyt Solution (Cytec, MA, USA) and sent to the pathology laboratory for cytological classification which was performed by an experienced cytopathologist. Smears were prepared from PreservCyt Solution taken under sterile conditions. The remaining solution was immediately sent to the molecular microbiology laboratory for detection of HPV. Cytopathologic classification of smears as LSIL and HSIL were performed according to the Bethesda classification. Cervical biopsies were taken from patients whose cytologic examinations were classified as HSIL and also from some patients with HR-HPV DNA positivity whose cytological examinations were classified as LSIL. Histopathologic examination results were classified as LSIL for CIN1 lesions and HSIL for CIN2 and CIN3 lesions.

Nucleic acid isolation: Isolation of nucleic acid from endocervical scrape specimens in PreservCyt Solution, was performed with vacuum manifold QIavac 24 plus (Qiagen Valencia, CA, USA); 250 μ l of material was used with Amplilute liquid media extraction kit (Roche, Applied science) as described by the manufacturer. Nucleic acid was eluted in a final volume of 120 μ l. Fifty microliter of this extract

was added to the master mix for the amplification reaction.

Detection of HPV DNA: The Amplicor HPV test was used which detects 13 high risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) with a multiplex amplification and colorimetric detection following hybridization.

Amplification of HPV DNA: The test amplifies a sequence which is approximately 165 bp in length within the polymorphic L1 region with 12 primers. An additional primer pair amplifies a fragment in the human β -globin gene as an internal control which evaluate the presence of PCR inhibitors and check the adequacy of the sample. The master mix also included Uracil-N-glycosylase enzyme and deoxyuridine triphosphate (dUTP) for prevention of false positivity arising from previous PCR runs. Fifty microliters from the extracts were added to the master mix and amplification reactions were carried out in TC9700 thermal cycler (Perkin Elmer) as suggested by the manufacturer.

Hybridization reaction: After PCR amplification, the HPV amplicon and the β -globin amplicon are chemically denatured to form single-stranded DNA by the addition of denaturation solution. The biotin-labeled HPV and β -globin amplicons are hybridized to the oligonucleotide probes bound to the wells of a multiwell plate. This hybridization reaction is another step increasing the specificity of the test.

Detection reaction: Following the hybridization reaction, the plate is washed to remove unbound material and Avidin-Horseradish Peroxidase Conjugate is added to each well. The Avidin-Horseradish Peroxidase Conjugate binds to the biotin-labeled amplicon hybridized to the oligonucleotide probes bound to the wells. The wells are washed again to remove unbound conjugate and a substrate solution containing hydrogen peroxide and 3,3',5,5'-tetramethylbenzidine (TMB) is added to the wells. In the presence of hydrogen peroxide, the bound horseradish peroxidase catalyzes the oxidation of TMB to form a colored complex. The reaction is stopped by addition of a weak acid and the absorbance at 450 nm is measured using an automated microwell plate reader.

RESULTS

The patients characteristics are shown in Table 1.

High risk HPV DNA positivity rates: A total of 208 samples (174 from patients with abnormal Pap smear results and 34 from control cases) were tested. β -globin was negative for 45 samples. The frequency of HR-HPV positivity according to Pap smear results is shown in Table 2. Among the samples with an amplified β -globin, 39 were found positive for HR-HPV DNA. HR-HPV DNA rates for control cases, LSIL

Table 1: Patients characteristics

Characteristics	Normal (%)	LSIL (%)	HSIL (%)	Total
Age (mean/range/SD)	41.8/20-59/8-7	47.6/20-84/11-7	52.5/27-77/10-8	47.61/20-84/11.50
History of pregnancy				
0	2 (13)	12 (80)	1 (7)	15
1-2	25 (20)	80 (64)	20 (16)	125
≥ 3	7 (10)	42 (62)	19 (28)	68
Smoking				
Yes	9 (22,5)	22 (55)	9 (22,5)	40
No	25 (15)	112 (67)	31 (18)	168
Oral contraceptive use				
Yes	4 (80)	1 (20)	0 (0)	5
No	30 (15)	133 (65)	40 (20)	203
Total	34	134	40	208

Table 2: Frequency of HPV positivity according to Pap smear results

Pap smear results	HR-HPV-DNA		Total
	Positive n (%)	Negative n (%)	
Normal	4 (23.5)	13 (76.5)	17
LSIL	19 (17.3)	91 (82.7)	110
HSIL	16 (44.4)	20 (55.6)	36
Total	39 (23.9)	124 (76.1)	163

Data represents only PCR results in which β -globin was positive. Difference of LSIL group with HSIL group was statistically significant ($p < 0.001$, Chi-square = 10.99)

and HSIL patients were 23.5% (4/17), 17.3% (19/110) and 44.4% (16/36) respectively and the difference between LSIL group and HSIL group was statistically significant ($p < 0.001$, chi-square = 10.99). The mean ages for HR-HPV DNA positive and negative cases were 46.38 ± 12.04 and 49.71 ± 11.08 years respectively and the difference between them was not statistically significant ($p = 0.111$). The HR-HPV DNA positivity percentage among tobacco users was 32.3% (10/31) and this rate was 22% (29/132) among non-users. The difference between them was not statistically significant ($p = 0.246$). Because of the low rate, comparisons for oral contraceptive usage was not made. The positivity rate for cases without a pregnancy was 63.6% (7/11) and it was statistically different from cases with a history of pregnancy (20.38%, 32/152, $p = 0.0001$).

When women who have Pap smear test results classified as HSIL were compared in smokers (29%, 9/31) and non-smokers (21.7%, 31/143 $p=0.48$), and in cases with (24.4% 39/161) and without a pregnancy history (7.7%, 1/13), the difference was not statistically significant ($p = 0.48$ and $p = 0.303$ respectively). When the mean age of HSIL cases (52.5 ± 10.83) was compared with LSIL cases (47.63 ± 11.68) there was a statistically significant difference ($p = 0.0001$).

Histological examinations were made for 13 out of 16 patients who were found positive for HR-HPV

DNA histologically classified as HSIL. All the 13 samples were CIN2+ lesions (6 cervical squamous cell carcinoma, 4 CIN3, 3 CIN2). Out of 20 HSIL and HR-HPV DNA negative patients histological examination results were available for 17 cases and only four out of them were classified as CIN2. From the other samples six were CIN1, six were chronic cervicitis and one was radiotherapy related degeneration. The difference between HR-HPV DNA negative and positive group was statistically significant ($p = 0.0001$). For HSIL patients, 13 out of 17 with CIN2+ lesions were positive for HR-HPV DNA (sensitivity: 76.5%, positive predictive value: 100%) and all of the 13 patients who had lesions other than CIN2+ were negative for HR-HPV DNA (specificity: 100%, negative predictive value: 76.5%). Histological examination results for HSIL patients are summarized in Table 3. Only seven out of 19 samples with LSIL and HR-HPV DNA positivity were available for histological examination and three out of them were CIN2+ lesions (one squamous cell carcinoma, two CIN2 lesions). From the other four samples one was found normal, two samples were CIN1 and one sample was chronic cervicitis.

DISCUSSION

HR-HPV DNA positivity rate was 23.97% (35/146) among patients with abnormal Pap smear test

Table 3: Histological examination and HR-HPV DNA positivity rates for HSIL patients.

HR-HPV DNA	Histological examination		Total
	CIN2+ n (%)	Others n (%)	
Positive	13 (100)	0 (0)	13
Negative	4 (23.5)	13 (76.5)	17
Total	17	13	

Data represents only PCR results in which β -globin was positive. The difference between HR-HPV DNA negative and positive group was statistically significant (p value < 0.001 , Chi-square = 17.54)

results. This rate was 14.7 and 80% in different regions of Turkey^[9,10]. HR-HPV DNA rate for HSIL patients was 44.4% (16/36) in our study. This rate was much higher for studies made in industrially developed countries. A study from Vermont USA reported 384 HR-HPV DNA positive samples from 398 (96.5%) women who have Pap smear test results classified as HSIL^[11]. Another study from Austria found a lower positivity rate^[12]. This rate was found even lower (50%) in North-east Italy from 32 women who had Pap smear test results classified as HSIL^[13]. The reason for lower HR-HPV DNA positivity rates in HSIL patients found in this study can be the lower positivity rates of HR-HPV infections for the whole country when compared with industrialized countries. In this study four out of 17 (23.5%) healthy subjects were found to be infected with HR-HPV. This rate was very low from studies performed in different regions of Turkey when made with bigger populations, (ranging between 1.5 and 6.1 percent)^[14-16]. The infection rate for HR-HPV in healthy subjects was found to be 26.8% in USA^[17] and 14.3% in Belgium^[18]. When compared with the infectivity rates in industrialized countries, the infectivity rate found in our country is approximately 4 - 5 folds lower. In Muslim countries, age at first sexual intercourse tends to be later and lifetime and recent number of sexual partners also tends to be lower. These lifetime variables are strongly associated with HPV infections. Bhurgri *et al* found lower incidence of cervical cancer cases when compared with industrialized countries in South Karachi which is a Muslim region in Pakistan^[19]. Guidelines prepared for the managements of women with abnormal Pap smear tests are usually suitable for industrialized countries. Consensus guidelines prepared in 2006, recommend loop electrosurgical excision or colposcopy with endocervical assessment for managing women with HSIL^[20]. These procedures require trained and experienced personnel and raise the cost. In this study the biopsy results for all the 13 samples which were found positive for HR-HPV DNA and their Pap smear test results were classified as HSIL were CIN2+. Whereas only 4 of 17 patients with HR-HPV DNA negativity and HSIL cytology were found CIN2 and biopsies taken from the remaining 13 patients were classified as CIN1 or non-neoplastic abnormalities. In countries with different HPV infection epidemiologies, applying guidelines prepared in industrialized countries may result in unnecessary, invasive, time consuming and expensive procedures.

β -globin positivity rates were substantially lower when compared with other studies. Although this was 78.4% for our study, in other studies it was found to be 100%^[13] and 97.3%^[21]. Despite the fact that there can be so many reasons for β -globin negativity, the inadequacy of the material taken from endocervical scrapings seems to be the most probable reason. This

is supported with negativity rates increasing from HSIL samples to LSIL samples and being the highest for samples taken from healthy women. Also, all the samples found negative for β -globin gene, were studied repeatedly and found negative.

CONCLUSIONS

In Turkey, applying guidelines prepared in industrialized countries for the managements of women with abnormal Pap smear tests may result in unnecessary invasive procedures and increased costs. For formulating suitable guidelines we need more data from extensive and comprehensive studies representing the whole country. For the determination of the adequacy of the material studied we recommend to co-amplify β -globin gene with HR-HPV DNA. This co-amplification will prevent any false negatives which can result from insufficient sample collection.

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Original Article

Early and Mid-term Evaluation of Mechanical Heart Valve Replacement

Moaath Mousa Alsmady¹, Raed Mahmoud Ennab¹, Sohayb Sulaiman Hassuneh¹, Islam Mohammad Massad², Baseem Basheer Bustami³, Mahmood Abdalrahman AbuAbeeleh¹

¹Division of Cardio-Thoracic Surgery, Department of Surgery

²Department of Anesthesia

³Division of Cardiology, Department of Internal Medicine

Jordan University Hospital, Faculty of Medicine, University of Jordan, Amman, Jordan

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ABSTRACT

Objective: To investigate the operative mortality and mid-term (up to eight years) results of mechanical heart valve replacement

Design: Retrospective study

Setting: Jordan University Hospital, Amman, Jordan

Subjects: One hundred eighteen patients with valvular heart disease

Intervention : Mechanical valve replacement

Main Outcome Measures: Rate of complications and etiology of valvular heart disease

Methods: Retrospective data of 118 consecutive patients who underwent mechanical heart valve replacement from January 2001 to December 2008 at our institution was analyzed as

regards the early and late morbidity and mortality as well as for the etiology of valvular heart disease.

Results: The mean follow-up period was 52 months (range: 6 – 96 months). Hospital mortality was 2.5% (3 patients). Complications recorded during the follow-up study include: prosthetic valve endocarditis (3.4%), bleeding (3.4%), stroke (3.1%), and reoperation (0.8%). There was no structural valvular dysfunction. No patient had clinically significant hemolysis or valvular thrombosis. 81.2% achieved New York Heart Association class I or II status postoperatively.

Conclusion: Our data shows that heart valve replacement with mechanical valve can be performed with low morbidity and mortality and good outcome.

KEY WORDS: rheumatic heart disease, valve related complication

INTRODUCTION

Since their first implantations in 1977, bileaflet mechanical heart valves have shown a satisfactory hemodynamic performance and low complication rates. As a result the bileaflet prosthesis has become the valve model of choice when valve replacement with a mechanical device is contemplated^[1,2].

In western countries, valvular disease remains a common problem in the elderly, the most common etiology being degenerative, but in our part of the world, rheumatic valvular heart disease is still the most common cause.

Rheumatic heart disease is the most common cause of multivalvular disease in developing countries. Unless aggressive and timely intervention in the form of valve replacement is pursued, the condition progresses rapidly to disability and death.

Rheumatic fever and rheumatic heart disease had been decreasing in incidence in most developed countries, but worldwide it remains a very significant cause of cardiovascular morbidity and mortality. In

1994, it was estimated that 12 million persons suffered from rheumatic fever and rheumatic heart disease worldwide^[3]. A large proportion requires valve surgery within 5 to 10 years and many are children^[4].

Mechanical prostheses are used worldwide for valvular disease. However valvular replacement with a mechanical prosthesis carries the potential risk of thromboembolism and the need for life long anticoagulation with the attendant risk of hemorrhage.

The aim of this retrospective study was to analyze the in-hospital mortality and mid-term results of mechanical valve replacement (isolated or concomitant with other surgical procedures) at our institution.

SUBJECTS AND METHODS

We retrospectively reviewed the clinical records, outpatient records and surgical reports of all patients who underwent mechanical valve replacement (isolated or concomitant with other surgical procedures) at Jordan University Hospital, from January 2001 to

Address correspondence to:

Dr. Moaath Alsmady, MD. FRCS, Division of Cardio-thoracic Surgery, Department of Surgery, University of Jordan, PO Box 2086 Aljubiha, Amman, Jordan 11941. Tel : 0096265160737, Fax : 0096265353388, E-mail:moaath5@yahoo.com

Table 1: Baseline patient characteristics

Age (years) (mean \pm SD)	45.5 \pm 14.4 n (%)
Female sex	55 (47)
Male sex	63 (53)
NYHA class	
I-II	29 (25)
III-IV	89 (75)
Chest pain	69 (58)
Dyspnea	110 (93)
Syncope	10 (8.5)
Palpitation	45 (38)
AF	31 (26)
CAD	31 (26)
CHF	35 (30)
Renal failure	5 (4)
COPD	11 (9)
Previous Cardiac surgery	8 (7)
EF% (mean \pm SD)	48 \pm 10
DM	22 (19)
HTN	59 (50)
CVA	7 (6)
Endocarditis	4 (3.4)

NYHA = New York Heart Association, CHF = congestive heart failure, HTN = hypertension, COPD = chronic obstructive pulmonary disease, AF = atrial fibrillation, CAD = coronary artery disease, DM = diabetes mellitus, EF = ejection fraction, CVA = cerebrovascular accident

December 2008. We considered baseline characteristics including age, gender, cardiac symptoms, New York Heart Association (NYHA) functional class, presence of congestive heart failure, atrial fibrillation, diabetes, renal failure, chronic obstructive pulmonary disease, cerebrovascular accidents, previous cardiac surgery, coexistent coronary artery disease, mitral valve disease, endocarditis, and left ventricular ejection fraction (Table 1). Intraoperative variables such as cardiopulmonary bypass time, aortic cross-clamp time, size and brand of the implanted prosthesis, associated surgical procedures, and surgical priority were also included (Table 2). The operation was defined as urgent when the patient underwent surgery within seven days from the diagnosis, and could not be discharged home before the operation. Operative mortality was defined as death occurring within 30 days of cardiac surgery, or death prior to hospital discharge regardless of cause. Late mortality was defined as mortality after 30 days of cardiac surgery and hospital discharge. The valve related complications were defined according to the recently suggested guidelines for reporting mortality and morbidity after cardiac valve interventions, as hemorrhage, thromboembolism, prosthetic valve endocarditis, device thrombosis, structural valve deterioration and non-structural dysfunction including paravalvular leak^[5]. Operative complications and causes of death were recorded and analyzed.

Table 2: Operative Data

Data	n (%)
Surgical Procedure	
AVR	34 (29)
AVR + CABG	9 (8)
AVR + MVR	17 (14)
AVR+ MVR + CABG	1 (0.8)
AVR + Aortic aneurysm repair	3 (2.5)
MVR	49 (42)
MVR + CABG	5 (4)
Elective surgery	114 (97)
Urgent surgery	4 (3)
CPB time (mean \pm SD) (min)	101 \pm 30.1
Cross clamp time (mean \pm SD) (min)	69.9 \pm 20.1
Type of aortic valve	
Carbomedics	32 (50)
St.Jude	19 (30)
Medtronic	13 (20)
Type of mitral valve	
Carbomedics	17 (23.5)
St.Jude	51 (71)
Medtronic	4 (5.5)
Size of aortic valve	
19	5 (8)
21	29 (45)
23	23 (36)
25	7 (11)
Size of mitral valve	
27	30 (42)
29	32 (44)
31	9 (12.5)
33	1 (1.4)

AVR = aortic valve replacement, CABG = coronary artery bypass grafting, MVR = mitral valve replacement, CPB = cardiopulmonary bypass

The results of quantitative variables were expressed as means \pm standard deviation (SD). From January 2001 to December 2008, 118 patients underwent prosthetic valve replacement. Forty-six patients received a prosthetic aortic valve, 54 patients had a prosthetic mitral valve inserted and 18 patients had a double valve replacement. The entire population was made up of 63 men (53%) and 55 women (47%); mean age was 45 \pm 14 years. Valve diseases are presented in Table 3. Concomitant surgery was performed in 18 patients (15%). The most common procedures were coronary artery bypass grafting in 15 patients (13%) and replacement of the ascending aorta in three patients for aneurysm of the ascending aorta. Mean valve size was 22 \pm 2 mm for aortic valve replacement, and 28.5 \pm 2 mm for mitral valve replacement.

Operative technique

All patients were operated with cardiopulmonary bypass (CPB) under moderate hypothermia (32 - 34 °C). Cold-blood was used for myocardial protection.

Aortic valves were implanted with the leaflet axis perpendicular to the septum, whereas the mitral

Table 3: Causes of valve disease

Cause	AVR n (%)	MVR n (%)	Total n (%)
Rheumatic	39 (61)	58 (80.5)	97 (71.3)
Degenerative	14 (22)	9 (12.5)	23 (16.9)
Aneurysm ascending aorta	3 (4.6)		3 (2.2)
Endocarditis	6 (9.3)		6 (4.4)
Brucellosis endocarditis	2 (3.1)		2 (1.5)
Ischemic		5 (7)	5 (3.7)

AVR = aortic valve replacement, MVR = mitral valve replacement
 prostheses were implanted in reverse anatomic position.

Anticoagulation with heparin infusion was started 12 hours after surgery to keep a partial thromboplastin time ratio of 1.5 to 2.5. Sodium warfarin was given 24 hours after valve replacement to maintain an international normalized ratio (INR) level between 2.5 and 3.5. Heparin was stopped once the INR had reached the therapeutic level. After discharge the patients' anticoagulation regime was controlled at the hospital anticoagulation clinic.

RESULTS

One hundred and eighteen patients underwent mechanical valve replacement (isolated or concomitant with other surgical procedures) at our institution between January 2001 and December 2008. The mean age was 45.5 ± 14 (63 men, 55 women). Fifteen patients (13%) underwent concomitant CABG, and 18 patients (15%) underwent double valvular procedures. All except 29 (25%) patients were in NYHA class III or IV. Most common presenting symptoms were dyspnea on exertion or at rest in 110 (93%) and chest pain in 69 (58%) patients. Mean ejection fraction was $48 \pm 10\%$. The baseline values and operative data of study patients are shown in Table 1 and 2 respectively.

Rheumatic valvular disease was found to be the most common etiology of valvular lesion (97 patients, 71.3%), followed by degenerative disease in 23 (16.9%) patients (Table 3).

Operative mortality was 2.5% (3 patients). The first patient died intraoperatively due to uncontrolled bleeding and low cardiac output. The second patient succumbed to cardiac tamponade two weeks after surgery and the third patient died due to non-cardiac causes; he was on hemodialysis and died from sepsis and respiratory insufficiency two weeks after aortic valve replacement. Late death occurred in four cases. The cardiac causes of late death were congestive cardiac failure and arrhythmias in a patient with breast cancer two years after aortic valve replacement. Another patient died with prosthetic valve endocarditis 45 days after double valve replacement. Another patient died with congestive heart failure three months after

Table 4: Morbidities

Morbidity	n (%)
Stroke	4 (3.4)
Atrial arrhythmia	35 (30)
Re-exploration for bleeding	4 (3.4)
Prosthetic valve endocarditis	4 (3.4)

operation. One patient died suddenly 20 months after double valve replacement.

Early postoperative complications are listed in Table 4. The most common postoperative complication was atrial arrhythmia, which affected 30% patients.

In our study four patients (3.4%) developed stroke immediately post surgery and four patients developed bleeding (3.4%). There was one report of major hemorrhage accident (cerebral hemorrhage necessitating craniotomy) in a context of an INR greater than 5. The remaining three patients had minor bleeding (2 nasal and 1 urinary tract bleeding).

Four patients developed prosthetic valve endocarditis (3.4%). All had double valve replacement with bileaflet mechanical prostheses. Out of these four patients three were successfully treated with antibiotics and one died prior to scheduled reoperation because of congestive heart failure. One patient required reoperation for the implanted valves. The patient had a second aortic valve replacement because of a high pressure gradient of 40 mmHg. On exploration, no pannus in growth was found.

No structural valvular dysfunction was reported and no valvular thromboses were noted.

DISCUSSION

Approximately 210,000 patients, worldwide, undergo valve replacement surgery annually^[6]. Roughly, two-thirds out of this total have mechanical valves implanted. Accordingly, there is much ongoing investigation related to improving prosthetic valve construction. Bileaflet cardiac prostheses have shown a low incidence of complications and good hemodynamic performance.

The majority of our patients were less than 65 years of age and the cause of valvular disease was rheumatic. Hence the valve of choice remains a mechanical device.

The early (30 days, 2.5%) and late mortality (3.4%) rates in our series were comparable with those reported by other series of mechanical prostheses.

Conventional practice suggests that revascularization should be performed at the time of valve replacement if major coronary artery stenosis is present regardless of the presence or absence of angina^[7]. Reports indicate that myocardial revascularization does not increase the operative mortality of valve

replacement, and the functional result may be improved by relieving the symptoms of angina and providing improved myocardial protection^[8].

Aortic valve replacement has been shown to be associated with postoperative cerebrovascular accidents in approximately 10% of cases in several studies^[9,10]. This may be related to embolic events^[11,12]. This most devastating morbidity has a significant impact on survival and quality of life^[13]. We have routinely employed the technique of inserting a gauze into the left ventricle during excision of the native aortic valve with the aim of capturing embolic debris. In our study two patients (3.1%) developed stroke immediately post surgery.

The low occurrence of thromboembolic episodes in our patient population with the use of the mechanical valve prosthesis is noteworthy, the low incidence of thromboembolic events is presumably related to factors such as inherent difference in coagulable states^[14], and competence of the individuals managing the patient's anticoagulation. Also risk factors for thromboembolism are reduced in younger patients.

The need for lifelong oral anticoagulation therapy in patients with mechanical prosthetic valves is well-recognized. In patients not receiving long-term anticoagulation therapy, the average rate of major thromboembolism is estimated to be 4 to 8 per 100 patient-years^[15]. This risk is reduced to 2.2 per 100 patient-years with antiplatelet therapy, and further reduced to 1 per 100 patient-years with oral anticoagulation (warfarin). Thus, the utilization of postoperative warfarin therapy reduces the incidence of major embolism by approximately 75% and has become the standard of care for all patients with mechanical prostheses^[15].

The American College of Cardiology / American Heart Association and the American College of Chest Physicians recommended, in their most recent guidelines, that contemporary mechanical valves in the aortic position be anticoagulated with a target INR of 2.0 to 3.0, and mechanical valves in the mitral position be anticoagulated with a target INR of 2.5 to 3.5^[16].

The American College of Cardiology / American Heart Association, in their most recent guidelines, recommended that the addition of aspirin (80 to 100 mg/day) to warfarin be strongly considered for all patients with mechanical valves^[16].

Concerning the localization of bleeding; the most common sites of minor bleeding are the nose and mouth, accounting for over one-third of episodes and the gastrointestinal tract is the most frequent source of major bleeding^[17]. In our study, three minor bleeds (75%) occurred in the ENT-tracts and one major bleed was intracerebral hemorrhage. We adhered to a low-intensity anticoagulation regimen in which a target

international normalized ratio (INR) in isolated aortic valve replacement (AVR) was 2 to 2.5 and in double valve replacement was 2.5 to 3.0.

Prosthetic valve endocarditis remains a serious complication of heart valve surgery despite improvements in prophylaxis, diagnosis, and treatment. The traditional approach to the management of this condition has been early surgery. Superior results have been shown with surgical treatment compared with antibiotics alone. However, while early surgery is indicated in patients with hemodynamic compromise, there is evidence that in selected cases treatment with antibiotics alone provides equivalent results^[18].

Structural deterioration resulting in mechanical failure of the prosthesis did not occur. The review of the literature of Orsinelli and colleagues^[17] reported six isolated cases of leaflet embolization and one case of leaflet fracture^[19].

The risk of prosthesis-patient mismatch (PPM) is most commonly encountered in patients undergoing aortic valve replacement (AVR) for severe calcified aortic valve stenosis, a typical disease of ageing. Nearly thirty years after the pioneering study by Rahimtoola^[20] the effects of PPM are still controversial. Some authors maintain that increased transvalvular gradients after aortic valve replacement may hamper the regression of the left ventricular mass^[21].

Mariano Vicchio and colleagues^[22] have reported the presence of severe or moderate patient-prosthesis mismatch, although occurring in a large proportion of patients receiving small size bileaflet aortic valve prostheses, did not influence long-term outcome, left ventricular mass regression, and quality of life..

There was no instance of paravalvular leak in the present review. We believe that interrupted horizontal mattress sutures with Teflon pledgets are a *sine qua non* in its prevention. Clinically significant hemolysis is almost always associated with the presence of detectable paravalvular leaks. In our study there was no case of clinically significant hemolysis. We did not look at subclinical hemolysis. We routinely put our patients on folic acid supplement daily.

A controversial point remains regarding the inclusion of sudden death in the valve-related deaths. The significant risk factors on univariate analysis were known preoperative ventricular arrhythmias and associated coronary artery disease. Although suggestive, univariate analysis does not prove a direct relationship between arrhythmias and sudden death. Here again, none of the valve-related factors have been identified as risk factors. This finding is in agreement with two recent autopsy studies questioning the value of classifying sudden death as valve-related death. Rooney and colleagues^[23] showed in 48 autopsies after sudden deaths with the Medtronic Hall valve (Medtronic, Inc., Minneapolis, Minn.) that 90% of deaths were unrelated

to the prosthesis, and Burke and coworkers^[24] found among 37 patients with sudden death that more than half of the deaths were due to cardiac hypertrophy and atherosclerosis, hypothesizing a relationship with ventricular arrhythmia

The NYHA functional status of surviving patients significantly improved when compared with their NYHA grade before surgery. Whereas 75% of patients were in NYHA class III or IV preoperatively, 81.2% achieved class I or II postoperatively.

Echocardiographic functional assessment six months after operation showed improvement in ejection fraction from an average baseline value of $48 \pm 10\%$ to about $52 \pm 10\%$.

The main limitation of the present study resides in its retrospective design.

CONCLUSION

Our data shows that valve replacement with a mechanical valve may be performed with low morbidity and mortality.

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Case Report

Heterotopic Pregnancy after Clomiphene Citrate Ovulation Induction - A Case Report

Mohsen Abdel Rahman, Amal Khader Ayed

Department of Obstetrics and Gynecology, Farwania Hospital, Kuwait

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ABSTRACT

Clomiphene citrate (CC), is widely used in the primary care setting to treat anovulatory infertility. However, CC has a reported multiple pregnancy rate of 11%. While triplets and higher order pregnancies resulting from clomiphene are rare on an individual basis, CC does have a significant impact on the overall incidence of higher order pregnancies owing to its wide use. This report describes a case of quadruplets pregnancy after ovulation induction with CC complicated by three intrauterine fetal demise and heterotopic disturbed tubal pregnancy. Early diagnosis of heterotopic pregnancy is important to decrease maternal mortality and morbidity and to preserve future fertility. Ovulation induction with

CC should only be performed in circumstances which allow access to ovarian ultrasound monitoring. The Royal College of Obstetrics and Gynecology (RCOG) guidelines recommend that CC use should be monitored with ovarian ultrasound. Such monitoring is not currently routine practice. If primary care is involved there should be an agreed shared care protocol. Moreover, patients undergoing ovulation induction must be given information about the risk of multiple pregnancies after CC. Early ultrasound is important for early diagnosis of heterotopic pregnancy, to decrease maternal mortality and morbidity and to preserve future fertility.

KEY WORDS: clomiphene citrate, multiple pregnancy, ultrasound

INTRODUCTION

Multiple pregnancy and ectopic pregnancy are recognized complications of ovulation induction. Both complications are increasing since the advent of assisted reproductive technology involving the use of supraovulatory drugs and the availability of high resolution ultrasound.

Clomiphene citrate (CC), which is widely used in the primary care setting to treat anovulatory infertility, is usually considered a safe drug^[1].

This report describes the case of an infertile anovulatory lady who presented with a combined multiple intrauterine and tubal pregnancy, and heterotopic pregnancy (HP), after ovulation induction with CC.

The commonly accepted incidence of HP is 1:30000^[2]. However the actual rate appears to be significantly higher^[2]. The most prominent reasons for increased incidence of HP are the wide and empirical use of CC, and increased incidence of ectopic pregnancy in fertile women together with the availability of highly sophisticated ultrasound machines.

CASE REPORT

A 27-year-old Egyptian patient was transferred to Maternity Casualty of Farwania Hospital, Kuwait, by an ambulance with history of dizziness followed by collapse at home just before her transfer. She had a regular 30 day cycle and her last menstrual period was reported to be nine weeks earlier. She conceived after one cycle of CC 50 mg daily on days 5 - 9 of the cycle and injection Human Chorionic Gonadotrophin (HCG) 5000 iu on day 13. Once pregnancy test was positive, she was given injection HCG 5000 iu weekly and cyclogest 400 mg vaginally daily. She had slight post coital blood loss per vaginum at seven weeks when an ultrasound scan detected a seven weeks viable intrauterine triplet.

Her obstetric history included one early fetal demise at 13 weeks for which evacuation of retained products of conception (ERPOC) was done one year ago. Her past medical history was irrelevant.

On examination, she was pale and sweating with cold extremities. Her pulse rate was 140 bpm and regular and her blood pressure was 90 /

Address correspondence to:

Dr Mohsen Abdel Rahman MRCOG, Department of Obstetrics and Gynecology, Farwania Hospital, P O Box 18373, Farwania 81004, Kuwait.
E-mail: mohsen.abd@hotmail.com

60 mmHg. She was found to have distended and tender abdomen and no apparent vaginal bleeding. She was resuscitated and emergency blood samples were sent for cross matching, full blood count, coagulation study and serum electrolytes.

An expedient ultrasound scanning (transabdominal and transvaginal) detected triplet intrauterine fetal demise (3 gestational sacs with fetal echoes in two but without cardiac pulsations). The left ovary was enlarged by multilocular cyst measuring 86.1 x 42.1 x 46.1 mm. There was large amount of fluid in the whole abdomen and pelvis including the sub-diaphragmatic region.

Her hemoglobin concentration was 8.6 g/dl and hematocrit was 26.3. The other blood test results were within the normal limits. The diagnosis was intra-abdominal hemorrhage due to either ruptured hyperstimulated ovarian cyst or disturbed HP was made.

An emergency exploratory laparotomy was performed. Blood was filling the abdominal cavity. The uterus was enlarged up to eight weeks size and there was ruptured left tubal pregnancy. The left ovary was enlarged, multicystic and intact. The right ovary and tube were normal. A left salpingectomy was performed. Hemostasis was secured. The abdomen was irrigated and closed. At the end cervical dilatation and evacuation of the uterus was done. The histopathologic examination confirmed the presence of both intrauterine and tubal pregnancy.

The patient received four units of cross-matched packed RBCs. She was discharged well on the 5th post operative day with a follow-up plan.

DISCUSSION

HP is defined as the simultaneous occurrence of an intrauterine and ectopic pregnancy^[1]. Heterotopic pregnancy is potentially dangerous for the mother and for the intrauterine pregnancy^[2]. In a spontaneous conception, HP is a rare event. The risk of HP significantly increases after ovulation induction^[3].

CC is the treatment of choice in women with ovulatory disorders who have normal estrogen levels^[4]. After CC induction of ovulation, the rate of multiple pregnancy and HP are increased^[4]. CC which increases the rate of twinning could be associated with a HP rate of 1 / 900^[5].

The challenge with management of ectopic pregnancy is early diagnosis. In an isolated ectopic pregnancy sonographic evidence of empty uterine cavity combined with a HCG concentration of higher than 1500 mIU / ml is the principal indicative factor. In the case of HP the early diagnosis of ectopic pregnancy is difficult. Therefore, it is not surprising

that most HPs are only diagnosed following rupture and hemorrhagic shock^[6]. Delay in diagnosing the condition can jeopardize both maternal well-being and survival of the intrauterine pregnancy^[7]. Management of HP involves salpingectomy or salpingostomy through either laparoscopy or laparotomy depending on the patient's condition, accuracy of diagnosis and availability of expertise in laparoscopic techniques.

In our case, an emergency laparotomy was performed as the patient's condition was jeopardized. Salpingectomy was unavoidable due to the degree of the tubal damage.

Less invasive techniques have been described to treat HP. They include injection of potassium chloride^[8], hyperosmolar glucose^[9] and potassium chloride together with methotrexate^[10] into the ectopic gestation under ultrasound guidance. These techniques achieved varying success rates in the management of ectopic pregnancies.

CONCLUSION

The risk of HP has increased after the widespread use of ovulation induction therapies and assisted reproductive techniques.

CC which increases the rate of twinning could be associated with a HP rate of 1 / 900. When an ectopic gestation is suspected after induction of ovulation by CC, the presence of an intrauterine pregnancy can no longer be considered reassuring and a HP has to be ruled out.

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Case Report

Beta-Ketothiolase Deficiency in an Indian Patient Living in Kuwait

Osama AAM El-Hashash, Tarek MM Seoudi, Hany M Nadi

Department of Pediatrics, Farwania Hospital, Kuwait

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ABSTRACT

Beta-ketothiolase (BKT) deficiency is a rare inborn error of isoleucine and ketone body metabolism. Its clinical manifestations range from an asymptomatic course to severe life-threatening ketoacidotic attacks with coma and cardiomyopathy. Early diagnosis and proper management may save lives of several patients, prevent neurodevelopmental complications

and lead to favorable outcome. We report this case of a twenty-month-old Indian boy with BKT deficiency. This is to alert pediatricians to this rare metabolic disorder and to consider it in patients presenting with metabolic acidosis. To the best of our knowledge this is the first case to be reported from Kuwait and also from India.

KEY WORDS: inborn errors of metabolism, metabolic acidosis

INTRODUCTION

Beta-ketothiolase (BKT) deficiency is a rare autosomal recessive inborn error of isoleucine and ketone body metabolism^[1]. Daum *et al* first described the disease in 1971. They found increased urinary level of alpha-methyl-beta-hydroxybutyric acid in a patient who presented with recurrent severe metabolic acidosis. They suggested that the disorder is due to enzymatic deficiency in the pathway of isoleucine catabolism^[1]. BKT enzyme was directly demonstrated to be deficient in skin fibroblasts by Robnison *et al* in 1979^[2].

The clinical manifestations range from an asymptomatic course to severe life threatening ketoacidosis with coma and cardiomyopathy^[3-5]. Over 40 cases have been dealt with in publications and more than 20 other patients have been reported. There is no particular ethnic predisposition. Patients have been reported from Europe (France, Germany, Italy, Netherlands, Norway, Spain, Switzerland, United Kingdom) the Americas (Brazil, Canada, Chile, USA), the Middle East (Israel, Saudi Arabia, Yemen), and Asia (Japan, Laos, Vietnam)^[6].

This report describes a twenty-month-old Indian boy, living in Kuwait, with BKT deficiency.

CASE HISTORY

A twenty-month-old boy presented at the age of fourteen months with his first attack of lassitude, excessive tiredness, drowsiness and altered

consciousness. This was preceded by symptoms of upper respiratory tract infection associated with refusal of feeding and repeated vomiting for about two days. He had no history of fever, convulsions, skin rash, and exposure to ill patients or recent travel. He was born at term after an uneventful pregnancy through normal vaginal delivery with no neonatal problems. He was fed artificial cow's milk formula with regular mixed diet introduced at the age of five months.

His parents are distant relatives with no history of abortions and neonatal or unexplained deaths in the family. He has two healthy siblings.

On admission to the hospital he was afebrile, ill looking, with shallow rapid breathing. His height, weight and head circumference were just below the 5th percentile for age. Chest, heart and abdominal examination revealed no abnormality apart from tachypnea and tachycardia. His blood pressure was normal for his age.

He looked ill, sleepy and drowsy but arousable and was responding to voice with eye opening and to painful stimuli with crying. Tone, power and reflexes were normal. Investigations showed mild hyperglycemia (9.2 mmol/l, range - 3.9 - 6.1 mmol/l), normal levels of serum urea, electrolytes, ammonia, lactate, renal and liver function tests and normal anion gap. Complete blood count showed white blood cells of $13.7 \times 10^9/l$ (neutrophils 76%, lymphocytes 17.3%), hemoglobin of 105 g/l, mean corpuscular volume of 67.5 fl and platelets of $485 \times 10^9/l$

Address correspondence to:

Dr. Osama El-Hashash, MRCPCH (UK), PO Box 1940, Al Ardiya, Kuwait 92400. Tel: 24753871, Fax: 24893318, E-mail address: osama_elhashash@hotmail.com

Cerebrospinal fluid (CSF) examination was normal. Capillary blood gas analysis showed pH 7.07, PCO_2 1.62 KPa, HCO_3^- 3.4 mmol/l and base excess of -24.5 mmol/l, with ketones 4+ in urine. Urine for organic acids and blood spots on filter paper were collected for Tandem Mass spectrometry. Both of them revealed high levels of tiglylglycine and 2-methyl-3-hydroxybutarate consistent with the diagnosis of BKT deficiency. Tandem Mass spectrometry screen in blood and urine for parents and both siblings were normal while they were asymptomatic.

The child was managed with intravenous 10% dextrose and sodium bicarbonate cautiously to prevent iatrogenic hypernatremia until the attack was resolved over two days and was discharged on protein restricted diet (1gm/kg/day) and oral L-carnitine. On follow up after two and six months, he was doing well and his growth was catching up (weight crossed from below the 5th percentile to just below the 10th percentile for his age).

DISCUSSION

BKT deficiency is a rare autosomal recessive metabolic disorder. It is due to deficiency of mitochondrial acetoacetyl-CoA thiolase (T2) which is responsible for cleavage of 2-methylacetoacetyl CoA to acetyl CoA and propionyl CoA in the pathway of isoleucine metabolism^[7]. It is also responsible for acetoacetyl CoA formation and cleavage in ketogenesis and ketolysis respectively. Hence ketone body metabolism and isoleucine catabolism are disturbed in this disorder^[6].

Clinical manifestations are quite variable, ranging from an asymptomatic course in an adult to severe episodes of acidosis starting in the first year of life^[7]. Patients usually have no clinical symptoms in the neonatal period and early infancy. In most cases the first ketoacidotic attack occurs when they are between five months and two years of age. Ketoacidotic events usually follow gastroenteritis, prolonged fasting and/or febrile illness such as upper respiratory tract infection, measles or otitis media^[6]. Our patient was delivered normally and had normal neonatal period. He developed his first ketoacidotic attack at the age of 14 months that was precipitated by upper respiratory tract infection, vomiting and refusal of feeding for two days.

Clinical symptoms of ketoacidotic crisis include: vomiting, dehydration, polypnea and / or dyspnea, hypotonia, lethargy and twitches, sometimes followed by coma. Some patients develop convulsions^[6].

Acidosis is typically severe (pH < 7.1, HCO_3^- < 7) and glucose is generally normal, but hypoglycemia and hyperglycemia have been described. Moderate hyperammonemia and hyperglycinemia can occur^[8].

Investigations in our patient showed severe metabolic acidosis, mildly raised blood glucose and normal serum ammonia. Diagnosis of BKT deficiency depends on suggestive clinical picture and elevated metabolites in blood and urine. It is confirmed by direct enzyme assay in fibroblasts, peripheral blood lymphocytes and polymorph nuclear cells. The urine metabolites are variable^[8]. It contains large amount of 2-methylacetoacetate (2Me-AcAC) and its decarboxylation product butanone, 2-methyl-3 hydroxybutarate (2Me-3HB) and tiglylglycine^[7]. Elevation of 2Me3HB is the most consistent finding^[8]. Although in most cases the urinary organic acid pattern during or between the attacks is diagnostic, it is difficult to rule out BKT based only on a normal metabolite pattern in a sample during an asymptomatic period^[8].

Our patient was diagnosed depending on clinical picture and typical elevated metabolites in urine and blood. Family screening for the metabolites in the asymptomatic parents and siblings was negative. Unfortunately, enzyme assay was not available in our area. Although diagnosis was confidently given to the patient (depending on raised metabolites in urine and blood), it was not ruled out in his parents or siblings.

Treatment of acute episodes includes hydration and infusion of bicarbonate cautiously to correct the acidosis. A 10% glucose solution with appropriate electrolytes may be used to minimize the catabolic state. Peritoneal dialysis may be required if the above measures did not produce significant clinical improvement. For long term therapy restriction of protein intake (1-2 g/kg/day) and L-carnitine (50-100 mg/kg/day) supplementation to prevent possible carnitine deficiency^[7] and to facilitate excretion of accumulated acyl-coAs as acylcarnitines in urine is recommended^[6].

Overall, the prognosis for normal development is excellent with therapy if neurological damage has not occurred prior to diagnosis. In a summary of a literature review of 26 patients, two had neurological abnormalities prior to developing a ketoacidotic crisis (one remained severely retarded whereas the other regained normal development) and four developed ketoacidotic attack (one died of hypernatremia and cerebral hemorrhage, one was slightly retarded, two showed delayed development after the attack but recuperated and had normal intelligence on follow-up). The other patients had not developed ketoacidotic episodes while on treatment^[8].

Our patient was managed successfully with intravenous 10% glucose and cautious correction of metabolic acidosis with intravenous bicarbonate during his first episode and was discharged on oral L-carnitine and on a diet that contains 1gm /kg /day protein.

His follow up over a six months period revealed normal development and his weight crossed the percentiles from below the 5th to just below the 10th percentile for his age.

CONCLUSION

BKT deficiency is a rare inborn error of isoleucine and ketone body metabolism. It usually has a favorable outcome and its clinical consequences can be avoided by early diagnosis, appropriate management of ketoacidotic attacks and modest protein restriction.

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Case Report

Budd-Chiari Syndrome with Hematemesis at Presentation

Kholouda Ahmed Abdullah, Ashraf Gaber Kishk, Amal Ali Nasr
Department of Internal Medicine, Al-Amiri Hospital, Kuwait

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ABSTRACT

The deficiency of protein C and protein S has been implicated in the etiology of Budd-Chiari syndrome. We present a case of young man who presented with life-threatening upper gastrointestinal bleeding. The

final diagnosis was Budd-Chiari syndrome. We review current information regarding the clinical aspects of this condition.

KEY WORDS: liver transplantation, portosystemic shunt, transjugular intrahepatic

INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare cause of portal hypertension, caused by thrombotic or non-thrombotic occlusion of the hepatic veins. It occurs in 1/100,000 in the general population^[1]. Budd described it in 1845 and Chiari added the first pathologic description of a liver with "obliterating endophlebitis of the hepatic veins" in 1899^[2].

The most common presentation is with ascites, but can range from fulminant hepatic failure to asymptomatic forms. Diagnosis is challenging. Medical therapy alone is usually ineffective. Radiological intervention such as transjugular intrahepatic portosystemic shunt (TIPS), or surgical interference, notably liver transplantation has emerged as the treatment of choice for patients with BCS^[3]. Prognosis is variable and depends on the age at presentation, degree of liver impairment and the presence of ascites. The aim of this case report is to increase awareness of this condition as a rare cause of portal hypertension in a young patient with unexplained liver cirrhosis.

CASE HISTORY

A 26-year-old man not known to have any medical problems was admitted to the intensive care unit with a one-day history of massive hematemesis. This was his first admission to hospital. On admission he was in shock but conscious, pale and not jaundiced. Vital signs revealed a blood pressure of 80/30 mmHg, pulse of 120 bpm and temperature of 36.0 °C. He had splenomegaly and ascites on abdominal examination. The rest of the examination was otherwise normal. Blood investigation results showed total peripheral white cell count of $4.5 \times 10^{10}/l$, hemoglobin of 5.4 g/dl, platelets count of $22 \times 10^9/l$

and an INR of 1.8. His renal as well as liver function tests were normal, apart from serum albumin of 23 g/l. He was resuscitated with a total of eight units of packed RBCs and eight units of fresh frozen plasma.

Urgent upper gastrointestinal endoscopy revealed grade III esophageal varices and bleeding fundal varix. After stabilization he was shifted to the medical ward. Abdominal ultrasound revealed coarse liver with irregular margins, splenomegaly and patent portal and hepatic veins. Hence, blood investigations were requested to find the cause of liver cirrhosis. They were negative for hepatitis B and C viruses, antinuclear antibody, anti-smooth muscle antibody and anti-mitochondrial antibody. Also, his ceruloplasmin was within normal range. As the cause of chronic liver disease in this young man was not clear, liver biopsy was done which showed preservation of the lobular pattern of the liver and normal hepatocytes in zones 1 and 2. However zone 3 showed hepatocyte loss and sinusoidal dilatation secondary to hepatocyte atrophy with extravasation of red cells into the space of Disse. Also, there was fibrosis with centro-central fibrous bridge formation in zone 3. These features are suggestive of chronic BCS (Fig. 1).

To assess the inferior vena cava (IVC) and the hepatic veins, computerized tomographic venography was done. This showed a patent IVC. The right hepatic vein was visualized except for a short segment just prior its entry into IVC suggesting a possible thrombosis. The left and mid-hepatic veins were not seen. The portal vein was normal. Extensive collaterals were noted (Fig. 2) and a thrombus was seen in the left renal vein (Fig. 3). Accordingly, thrombophilia screen was sent and

Address correspondence to:

Dr. Ashraf Kishk, MRCP (UK), Senior Registrar, Department of Internal Medicine, Al-Amiri Hospital, Kuwait PO Box 576, Alsouk Aldhagheli, Kuwait 15256. E-mail: akishk9@hotmail.com

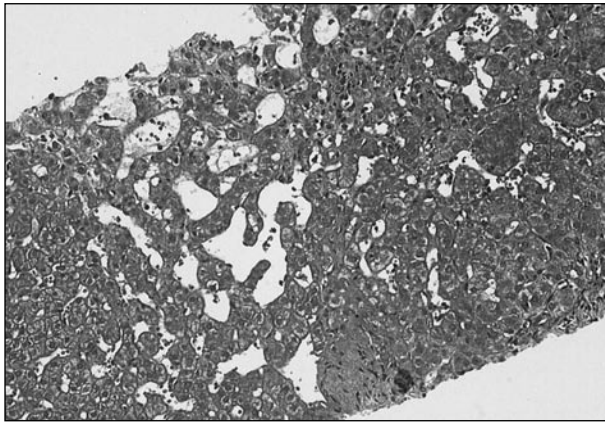


Fig. 1: Liver biopsy showing centrilobular necrosis, congestion and sinusoidal dilatation consistent with the presence of hepatic venous outflow obstruction

these showed protein C of 47.5% (normal value = 70 - 140%) and protein S of 53.7% (normal value = 60 - 140%) The rest of the screen was normal. He was started on oral propranolol and spironolactone for the portal hypertension. Upper gastrointestinal endoscopy was repeated and this showed almost complete obliteration of the esophageal varices and non-bleeding fundal varix. Repeated coagulation profile was normalized and the patient was started on warfarin. He was discharged home well and advised regular follow-up.

DISCUSSION

Myeloproliferative disorders, particularly polycythemia vera are implicated in about half the cases of BCS. Thrombophilia are the next common cause, and 20% of cases are due to factor V leiden mutation^[4]. Deficiencies of protein C and S are other important contributing factors. However, the diagnosis of these protein deficiencies is not straightforward as the reduced concentrations may be caused by impaired liver synthesis. This patient had deficiency of both factors and this could be either secondary to his liver disease or due to an inherited

condition. In such a case familial studies are needed to prove the inherited origin. Also, BCS commonly affects women who use oral contraceptive pills with a relative risk of 2.37 as shown in a study by Mohanty *et al*^[5]. The syndrome has been described in both pregnancy and the postpartum period. Primary membranous obstruction of the IVC is an important treatable cause of BCS and this presentation is seen in about 60% of BCS cases in young adult men in Asia^[6]. Our patient was from this ethnic group and we ruled out this etiology by CT venography. In as many as 20% of cases of BCS no cause can be found. In these cases, a mutation in the JAK2 gene, which is associated with several types of myeloproliferative disorders, has been detected in a high proportion of patients with idiopathic BCS, providing further evidence that these patients have a latent myeloproliferative disorder^[7]. The BCS has three broad presentations: acute, subacute, and chronic. The clinical presentation depends upon the rapidity of hepatic vein thrombosis and the presence of collaterals. Abdominal pain, hepatomegaly and ascites are present in the majority of cases. Gastrointestinal bleeding (as in our case) occurs in 5 to 15% of patients as a presenting symptom and is responsible for most of the fatalities observed in this condition^[8]. However, asymptomatic cases have been described in patients in whom the liver sinusoids were decompressed by large portosystemic collaterals. Imaging plays a very important role in establishing the diagnosis of BCS. Doppler Ultrasonography of the liver is the initial imaging technique of choice with a sensitivity and specificity of 85%. However for better visualization of the hepatic veins and the configuration of the liver computed tomographic scanning (CT) should be done, especially, when TIPS is considered. This can show abnormal arterial enhancement of the caudate lobe, the so called "fan-shaped pattern" and this represents a characteristic finding of acute BCS. It may help to suggest the correct diagnosis even in the absence of visible venous thrombosis^[9].

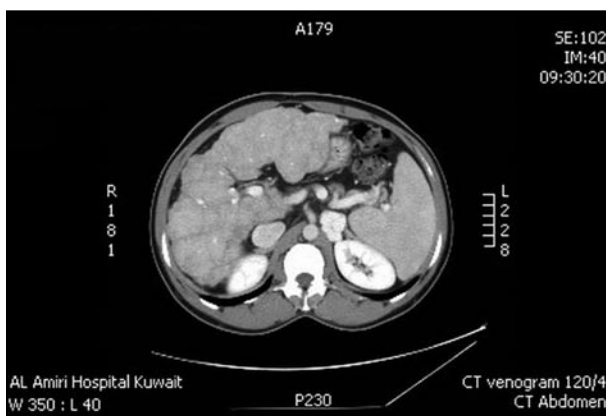


Fig. 2: CT venography showing non-visualization of a short segment of the right hepatic vein prior to its entry into IVC suggesting thrombosis

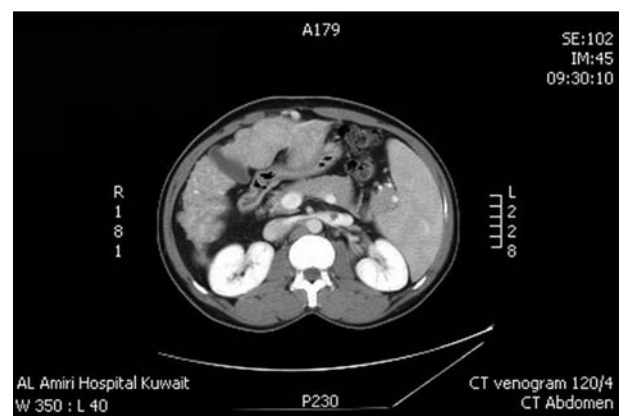


Fig. 3: CT venography showing thrombus in the left renal vein

Magnetic resonance images may be better than CT for complete visualization of the IVC and may help differentiate between acute and chronic forms of BCS. In this case however, liver ultrasonography was misleading and the hepatic veins were reported as normal. The correct diagnosis was made from liver biopsy. After establishing the diagnosis of BCS, there are three goals of therapy: to prevent propagation of the underlying thrombotic condition, to decompress the liver to prevent further ischemic damage and to relieve the ascites. All patients should receive anticoagulant to maintain an INR of at least 2.5. Short segment obstruction can be treated successfully by balloon dilatation or intravascular stent. Membranous web can be relieved by this method in 90% cases, but 20 - 30 % will need to repeat angioplasty due to recurrence of thrombosis^[10]. Failure of anticoagulation and angioplasty and the presence of diffuse hepatic vein thrombosis are indications for shunting. The principle of shunting is to convert the portal vein into a systemic circulation. A side to side mesocaval shunt not only decompresses the liver but also relieves the ascites and removes the risk of variceal bleeding. A pressure gradient between the portal vein and the IVC of 10 mmHg is essential for any shunting procedure^[11]. TIPS has improved the management of BCS. It avoids laparotomy, overcomes caudate lobe compression, and has lower periprocedure mortality than surgical shunting. TIPS does not preclude subsequent surgical shunting or liver transplantation. Long term patency after TIPS despite anticoagulation therapy only averaged 50%, with 36 - 72% of patients needing another intervention^[12]. TIPS may serve as a bridge to liver transplantation. Liver transplantation restores liver function in BCS and cures genetic defects of the coagulation pathways such as protein C and S deficiencies or antithrombin III deficiency. Other indications for liver transplantation include patients with fulminant liver failure and those with uncompensated liver cirrhosis^[13]. It was reported that with appropriate long term anticoagulation, 80% of patients with liver transplantation due to BCS had good graft survival at six-year follow up. Our patient was started on anticoagulant and he has responded well to this treatment as of now. However, if he did not respond, he will be a good candidate for liver transplantation especially in the presence of protein C and S deficiencies. Unfortunately this is not practical in his case due to his social background. BCS is a progressive disease with a mortality rate exceeding 75% if untreated. In the largest cohort of 237 patients, the severity of encephalopathy, ascites, prothrombin time and serum level of bilirubin resulted in defining patients with grave prognosis^[14]. In Japan, patients with membranous web in the IVC have a mortality rate of 25% over 15 years^[15].

CONCLUSION

BCS should be suspected in patients with unexplained portal hypertension, as it has a relatively good prognosis if treated appropriately.

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Case Report

Spontaneous Rupture of Splenic Artery Aneurysm during Pregnancy: A Rare Case with both Maternal and Fetal Survival

Mostafa Shoman, Khalid Al-Akkad
Department of Obstetrics and Gynecology, Al-Adan Hospital, Kuwait

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ABSTRACT

A case of spontaneous rupture of splenic artery aneurysm (SRSAA) during pregnancy is reported. In this particular case the diagnosis was reached only after cesarean section for suspected massive placental abruption following severe upper abdominal pain and

sudden fetal distress. Despite the abrupt and massive intraperitoneal haemorrhage with severe fetal distress, good maternal and fetal outcome could be achieved by early diagnosis, prompt management and active resuscitation.

KEY WORDS: pregnancy complication, rupture, fetal distress

INTRODUCTION

In the literature, more than 400 cases of spontaneous rupture of splenic artery aneurysm (SRSAA) have been reported, with a (reported) maternal and fetal mortality as high as 70 and 90%, respectively^[1], and, only in 14 instances, both maternal and fetal survival could be achieved^[2]. In almost all cases, the exact diagnosis was reached only during cesarean section (CS). This gives an idea about the rarity of the case and the difficulty in reaching a definitive diagnosis for these potentially life threatening problems. This case report is intended to increase awareness of this potentially lethal condition so that obstetricians can entertain the diagnosis of SRSAA in any pregnant woman presenting with severe upper abdominal pain with or without signs of maternal and fetal hypovolemia.

CASE HISTORY

A 31-year-old primigravida was admitted for induction of labour at 41-weeks gestation. She had no medical or obstetric problems. After receiving four doses of vaginal prostaglandin E2 tablets, 3 mg each 6 hours apart, to enhance cervical ripening, she developed sudden severe upper abdominal pain. She was transferred instantly to the delivery suite where she was carefully evaluated by the senior registrar on call. Her vital signs were stable. However, there was marked uterine tenderness and rigidity mainly over the upper abdomen and the fetal heart rate

was around 110 bpm. Pelvic examination showed no vaginal bleeding; the cervix was 70% effaced and 2 cm dilated and the fetal membranes were intact. Severe degree of placental abruption was suspected. Artificial rupture of fetal membrane was performed and direct fetal heart monitoring started. The amniotic fluid was clear. Standard initial resuscitative measures were commenced including fixing two large-bore IV cannulae, collecting blood samples for complete blood count (CBC) and grouping, saving four units of cross-matched blood and checking blood coagulation profile in addition to other standard investigations. The neonatologist, anesthetist on-call and the operating suite were all alerted about the case.

Ten minutes later, there was severe prolonged fetal bradycardia (about 80 bpm), with otherwise normal maternal vital parameters. An emergency CS was decided for fetal distress. The blood bank and the consultant hematologist were informed.

Once in the operating suite, the woman developed severe hypovolemic shock and active resuscitation and correction of the hypovolemia was commenced by the anesthetist. The abdomen was open through a vertical midline incision and the peritoneal cavity was found filled with about two liters of fresh blood. At this stage, uterine rupture was suspected, although it was considered unlikely in a primigravida not in active labor. The consultant obstetrician was called and the baby was delivered without delay. As expected, there was neither placental separation nor

Address correspondence to:

Dr Mostafa Shoman, P O Box 52028, Code 53461, Riqqa, State of Kuwait. Tel: + 965-23941626, Fax: + 965-23941626, E-mail: mshoman@canada.com

any retro-placental clots. Surprisingly the uterine wall was found intact and the bleeding was seen coming from the left part of the upper abdomen. A life-threatening major surgical emergency was suspected, possibly spontaneous rupture of spleen or liver, and the hospital emergency team was called instantly through hospital emergency code.

Thorough exploration of the abdominal organs by a consultant surgeon revealed profuse bleeding from a ruptured distal splenic artery aneurysm and a large lesser sac hematoma. Splenectomy, evacuation of the haematoma and ligation of the splenic artery proximal to the site of rupture was done and proper hemostasis was finally achieved. The operation time was about two hours. These surgical steps were done simultaneously with active volume replacement, blood transfusion, vital signs monitoring and correction of depleted coagulation factors by the anesthesia team together with the hematologist. The patient received a total of 13 units of packed red blood cells, eight units of fresh frozen plasma and six units of platelets.

The newborn was a live girl weighing 3312 grams. At delivery she was pale and flaccid with low Apgar score (3 and 6 at 1 and 5 minutes, respectively). Cord blood pH was 6.950 with -24 mmol / l base excess. Active resuscitation was carried out by the neonatologist, after which the baby was admitted to the neonatal intensive care unit (NICU) for further management.

Subsequently, the patient had an uneventful postoperative period. After an initial observation in the intensive care unit (ICU), she was transferred to the regular ward on next day. She was discharged home on the seventh day, but the baby was kept for another four days before being discharged in good condition.

DISCUSSION

Although more than 400 cases of SRSAA have been reported in the literature, the reported maternal and fetal mortality was as high as 70 and 90%, respectively^[1], with only 14 instances where both maternal and fetal survival could be achieved^[2]. The devastating consequences and poor outcome of this condition is related mainly to its rarity as well as being often misdiagnosed as either uterine rupture or rupture of the spleen. Therefore the diagnosis is

usually reached after CS as an obstetric emergency. Once diagnosed, management decisions are clear-cut and uncontroversial. Active resuscitation and arrest of hemorrhage are the key elements necessary for the survival of both mother and fetus^[3]. Splenectomy is often performed in addition to resection of the aneurysm^[4-6]. For the obstetrician, it is imperative to involve the general or vascular surgeon as soon as SRSAA suspected.

CONCLUSION

In this case, survival of both mother and fetus was made possible mainly by the prompt decision for emergency CS for fetal distress even before the onset of labor, prompt awareness of the emergency/resuscitation team, effective blood banking service, and a consultant level care. Furthermore, this case enforces the advice that the diagnosis of SRSAA should be considered in any pregnant woman presenting with severe upper abdominal pain with or without hypovolemic shock. Obstetricians should be aware of the prodromal and catastrophic consequences of SRSAA. It is essential for the obstetricians to have a high index of suspicion with early recognition and prompt management, including early involvement of a general surgeon in order to achieve maternal and fetal survival.

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Case Report

Persistent Fetal Bradycardia - A Marker for Inherited Metabolic Disorder?

Ramadevi V Wani¹, Usha Rajaram², Sami Al Taher¹¹Department of Obstetrics and Gynecology, Al Jahra Hospital, Kuwait²Department of Pediatrics, Al Jahra Hospital, Kuwait

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ABSTRACT

This case report highlights the persistent fetal bradycardia without fetal distress presenting at 29 weeks gestation. Approach to etiological diagnosis is discussed. The

neonatal inborn error of metabolism as a cause for this bradycardia is emphasized.

KEY WORDS: fetal echocardiography, primary lactic acidosis

INTRODUCTION

Persistent fetal bradycardia defined as heart rate of less than 100 per minute^[1] is infrequent in prenatal life^[2]. Persistent fetal bradycardia without fetal distress needs evaluation and proper choice of management options. The overall fetal well being and clinical setting should be rapidly assessed to distinguish between fetal distress causing sinus bradycardia, which demands urgent delivery, from other causes of fetal bradycardia, to avoid unnecessary intervention. Once fetal distress is excluded the effective management of fetal bradycardia is dependent on the accurate assessment of the etiology. The differential diagnosis of fetal bradycardia not due to fetal distress includes sinus bradycardia, blocked premature atrial contractions, variable second degree AV block and complete heart block^[3]. Some of the more unusual causes are fetal effects secondary to maternal hypothyroidism, hypothermia or maternal administration of beta blocker^[4] and these can be diagnosed based on history, clinical examination and investigations. Echocardiographic assessment of the heart can give an accurate diagnosis in fetal bradycardia and provide a basis for appropriate obstetric management. Occasionally, a rare inborn error of metabolism may affect cardiac structure, function and the conducting system^[5]. We report here a rare case of primary lactic acidosis presenting as fetal bradycardia.

CASE REPORT

A 31-year-old Saudi lady, P2 + 0 + 4 + 1, was registered for antenatal care in our hospital. Her

first pregnancy ended as first trimester miscarriage. Second pregnancy came upto term and she delivered normally a male child who is alive and healthy. Third and fourth pregnancies ended in delayed miscarriage at 18 weeks and 10 weeks respectively. Fifth pregnancy was terminated by cesarean section at 38 weeks gestation, as there was intrauterine growth restriction (IUGR) with non-immune hydrops and persistent fetal bradycardia. The neonate died at the age of two days as a result of myocardial failure due to primary lactic acidosis. Sixth pregnancy ended as delayed miscarriage at 10 weeks gestational age. In view of this bad obstetric history, she was investigated. Tests for anticardiolipin antibodies and lupus anticoagulant were negative. Karyotyping of the couple revealed normal chromosomes in number and structure.

In the index pregnancy her last menstrual period was confirmed by early ultrasound. She was admitted to the hospital at 29+ weeks gestational age as clinically the fetus appeared small for gestational age. Non-stress test (NST) revealed persistent fetal bradycardia with baseline heart rate of 70 - 90 per minute with good variability and acceleration (Fig. 1). Fetal bradycardia was confirmed by ultrasound. Ultrasound also showed symmetrical intrauterine growth restriction with growth discrepancy of three weeks and no gross cardiac or other anomalies. A normal biophysical profile, umbilical artery Doppler study and maternal evaluation ruled out fetal distress. At 29 weeks pregnancy she had developed gestational diabetes and this was controlled with insulin. She was not on any medication known

Address correspondence to:

Dr Ramadevi V Wani, MRCOG, PO Box 17672, PC code 72457 - Khaldiya, Kuwait. Fax : +965-24577045, E-mail-ramawani@msn.com

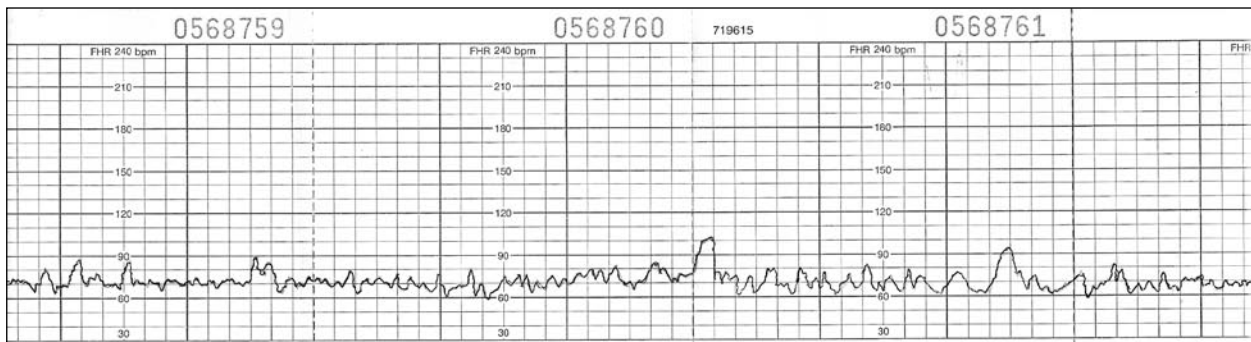


Fig.1. Fetal Non Stress Test done upon admission showing fetal bradycardia with good variability and accelerations

to cause fetal bradycardia. Fetal echocardiogram done by cardiologist at 31 weeks gestational age showed sinus bradycardia with normal intracardiac anatomy and infiltration of the endocardium and myocardium. There was no evidence of heart block. Fetal echocardiography repeated by perinatologist recorded normal sinus rhythm, normal heart structure and no features of cardiac failure.

The fetus was followed up in the ward with daily NST and weekly Doppler study. The NST showed persistent fetal bradycardia with good variability and accelerations. Fetal biometry continued to show a growth discrepancy of three weeks and the estimated fetal weight at 34 weeks of gestational age was 1643 ± 349 g. A decision to deliver the baby by cesarean section was taken to prevent the condition progressing to hydrops or intrauterine fetal death. The patient delivered a baby girl weighing 1340 g with an Apgar score of 2 / 6. The neonate was small for gestational age. There was no cardiac failure. However, she had severe lactic acidosis in the range of 17 mmol (normal range ≤ 2.2 mmol / l). The lactate to pyruvate ratio was high. Screening tests for fatty acid oxidation and organic acidemia were negative. The lactic acid showed an increase over 48 hours. In spite of bicarbonate, thiamine, biotin and medical management of severe academia, the baby died within 48 hours. The mother's blood gas analysis and lactic acid levels were checked and found to be normal.

DISCUSSION

Fetal cardiac output is dependent upon the fetal heart rate. Hence a persistent fetal bradycardia may lead to fetal congestive heart failure and hydrops which can lead to fetal death. Several maternal and obstetric conditions can cause 1:1 fetal bradycardia^[6]. Table 1 shows maternal and obstetric conditions causing fetal bradycardia. A detailed review of the case clinically and by laboratory investigations showed absence of the above etiology. Causes of persistent fetal bradycardia without fetal distress include arrhythmic or immunogenic causes. In our case the immunogenic causes of fetal bradycardia were ruled out by the absence of lupus antibodies.

Table 1 : Maternal and obstetric causes of fetal bradycardia with 1:1 conduction

Maternal

Medications - β blockers, amiodarone, Magnesium sulphate
 Medical disorders - hypothyroidism, hypertension, seizures
 Recreational drugs - cocaine
 Infections - chorioamnionitis
 Intrathecal anesthetics
 Non-obstetric surgeries
 Exercise
 Hypothermia
 Hypotension

Obstetric

Labour
 Cord prolapse
 External cephalic version
 Uterine rupture
 Fetal procedures like cordocentesis

Assessment for fetal arrhythmia needs state of the art fetal echocardiogram. Fetal echocardiogram uses all modalities like 2D, M- Mode and Doppler, both pulsed and tissue. Some centers resort to fetal electrocardiogram and fetal magnetocardiography which are not available in our center. Fetal echocardiogram also shows structural heart defects and features of cardiac failure like increased cardiothoracic ratio, presence of pleural, pericardial effusions and ascites. A retrospective study by Boldt *et al*, over a period of 18 years showed that about 1% of fetuses present with arrhythmias^[7]. In this study of 292 cases of fetal arrhythmias, 50 had bradycardia out of which 33% had 1:1 atrioventricular conduction and 66% had atrioventricular block. In our case echocardiogram assessment by a cardiologist and fetal medicine specialist excluded structural cardiac defects or conduction defects. A normal rhythm of 1:1 atrioventricular contraction was seen in the fetus. There was no prolongation of the PR interval. There was no evidence of heart failure.

Decision regarding timing of delivery in case of persistent fetal bradycardia is challenging since the aim is to achieve reasonable maturity of the fetus without jeopardizing its health. This necessitates day

to day fetal assessment. Any early sign of cardiac failure or fetal hydrops calls for immediate delivery. In our case one of her siblings who had persistent bradycardia was delivered at 38 weeks of gestation due to the presence of hydrops fetalis and the baby had very high lactic acid level in the blood in the early neonatal period. The index case was delivered at 34 weeks in order to avoid the development hydrops fetalis. The neonatal course of the two siblings was identical. Postnatally, the babies had the same heart rate with 1:1 conduction on the electrocardiogram and no response to inotropes. The lactic acid was very high in both the babies, reaching levels of 55 mmol / l in the first baby with hydrops and 17 mmol (normal value \leq 2.2 mmol / l) in the index case.

Infiltrative cardiomyopathy with bradycardia is suggestive of an inherited metabolic etiology. The common metabolic conditions reported with infiltration in the myocardium include disorders of lysosomal enzymes like Gauchers, Hurlers and Pompe diseases. The presence of normal lysosomal enzymes in our study excluded these disorders.

The lactic acidosis may be primary due to the metabolic defect or secondary to reduced cardiac output and ejection fraction. However such elevated levels of lactic acid as found in our case are not the usual levels with lactic acidosis of compromised cardiac output with normal cardiac structure. Persistent fetal bradycardia due to inherited metabolic disorder is rare. In fact there is only one isolated case report in the literature. Buhner^[5] in 2003 reported a single case of fetal bradycardia at 28 weeks gestation caused by cardiac glycogen phosphorylase B kinase deficiency.

Primary lactic acidosis in neonates requires comprehensive analysis to establish the enzyme deficiency using clinical, biochemical, molecular and genetic studies. Tissue biopsy, histochemical and molecular studies are necessary for the exact diagnosis. However, in the absence of facilities for molecular studies, the standard algorithms^[8] can serve as a basis for deductions. In our two siblings there was absence of specific organic acidurias and fatty acid oxidation defects. The sonogram of the brain was normal. The presence of normal levels of lysosomal enzymes, increased lactate to pyruvate ratios, abnormal elevations of alanine and citruline in the blood aminogram and mild hepatomegaly in the two children in our report led us to infer that the lactic acidosis could be due to pyruvate carboxylase deficiency, type B. Type B presents in early neonatal period and the neurological deficits may not be evident in this period of life. Type A presents in infancy with neurological deficits and type C is the benign form presenting later in childhood.

To the best of our knowledge our case is the second case of inherited metabolic disorder in the literature presenting as persistent fetal bradycardia and this is the first case of fetal bradycardia reported in siblings.

CONCLUSION

Regional hospitals in Kuwait cater to closed communities living in a designated area. Autosomal recessive metabolic disorders are more evident due to high rate of consanguineous marriages between first cousins. Recent advances in the diagnosis and treatment of inherited metabolic disorders have improved substantially the prognosis for many of these disorders.

We recommend that prenatal metabolic screening with chorionic villi biopsy and fibroblast culture from amniotic fluid should be instituted for pregnant mothers presenting with unusual fetal heart rate patterns. The obstetrician turned perinatologist, the neonatologist and the pediatrician should be familiar with the clinical presentation of inherited metabolic disorders namely persistent fetal bradycardia, infiltrative cardiomyopathy and fetal hydrops.

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Case Report

Neonatal Meningitis Caused by *Salmonella Enteritidis* with Multiple Brain Abscesses – A Case Report

Shibu Thomas John, Mona Al Ajmi, Najeeb Al Othman
Pediatric Intensive Care Unit, Department of Pediatrics, Al Sabah Hospital, Kuwait

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ABSTRACT

Meningitis in neonates caused by the non-typhoidal salmonella, *S. enteritidis* is rare but is a rapidly progressive infection and may lead to irreversible brain damage. We report here a 10-day-old neonate with *Salmonella enteritidis* meningitis who presented with disseminated intravascular coagulation and central nervous system complications.

Blood, stool and cerebrospinal fluid (CSF) culture grew *Salmonella enteritidis*. CT brain done on the day of admission showed multiple supratentorial and infratentorial hypodense white matter lesions with dilatation of the ventricle. Rapid progression of the infection and the age would have contributed to the complications seen in our patient.

KEY WORDS: meningitis, neonate, *Salmonella enteritidis*

INTRODUCTION

In neonates meningitis caused by group B streptococcus, *Escherichia coli* and *Klebsiella* are much more common than that caused by *salmonella strains*^[1]. *Salmonella* meningitis carries a higher morbidity and mortality as compared to meningitis caused by other bacteria. Hence, early diagnosis and aggressive management is very essential to prevent long term complications and death. Due to the emergence of multidrug resistant strains of salmonella and the rapid progression of the disease, complications, mainly neurological are common^[1-3]. In neonates with *Salmonella* meningitis common neurological complications are seizures, hydrocephalus, subdural effusion, empyema, ventriculitis and cerebral abscess.

CASE HISTORY

Our patient was a 10-day-old Kuwaiti female neonate a product of full-term cesarean section delivery of a mother with history of previous cesarean delivery and no antenatal medical risk factors. Her birth weight was 2.9 kg and the baby was discharged home on the fourth day on formula feeds. The neonate was readmitted in the ward with a history of reduced oral intake for two days and fever and incessant cry for one day. There was no history of contact with any sick person at home. She was shifted to the pediatric intensive care unit (PICU) and was intubated and mechanically ventilated. Full septic work up was done. Blood culture grew *Salmonella enteritidis*. Lumbar puncture revealed yellow turbid CSF with

WBC 2578 / mm³ out of which 85% were neutrophils, RBC 8010 / mm³ and Sugar 0 mmol/l. Direct smear showed Gram negative bacilli and culture grew *Salmonella enteritidis* sensitive to cefotaxime and ciprofloxacin. The baby was very pale, lethargic with weak cry and had a bleeding tendency with a picture of disseminated intravascular coagulation (DIC). Her Hb was 8.6 g/dl, WBC 2 x10⁹/l, polymorphs 33%, lymphocytes 60% and platelet count 27 x10⁹/l. Coagulation profile showed PT 18 sec, APTT 35.7 sec and INR 1.64. Stool culture grew *Salmonella* species. She was started on cefotaxime 200 mg/kg/day and amikacin 15 mg/kg/day initially and other supportive measures. On receiving the culture and sensitivity results, ciprofloxacin injection in a dose of 10 mg/kg/dose twice daily was also added to the management. Lumbar puncture was repeated on the ninth day of antibiotic and the CSF which still grew *Salmonella enteritidis* sensitive to the given antibiotics. As the baby remained sick cefotaxime was changed to meropenem in a dose of 40 mg / kg / dose every eight hours and this was given for a duration of two weeks to which the baby responded well. Ciprofloxacin was continued for 21 days. The mother was screened and found to be free of salmonella infection.

CT brain done on the same day of admission showed multiple supra / infra-tentorial hypodense white matter lesions with dilatation of ventricles (Fig. 1). She developed seizures and was started on phenobarbitone and later epanutin was added. There was gradual improvement in the condition

Address correspondence to:

Dr. Shibu Thomas John, PICU, Dept of Pediatrics, Al Sabah Hospital, PO Box 4078, Safat 13041 Kuwait. Tel: +965-24838043, Fax: +965-24835805, E-mail: thomasdr68@hotmail.com

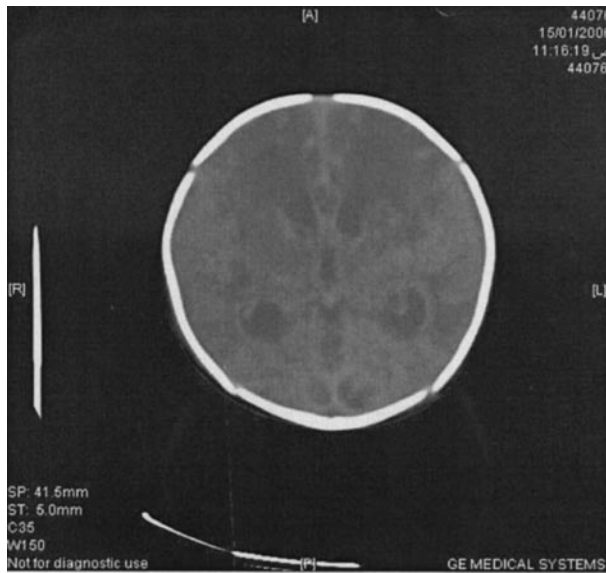


Fig. 1: CT brain showing multiple supra / infratentorial hypodense white matter lesion with dilatation of ventricles

and she was extubated after nine days of mechanical ventilation. After extubation she remained hypoactive and lethargic. Since other vital signs were stable, she was shifted back to the ward. MRI brain showed a picture of meningoencephalitis with ventriculitis and intraparenchymal abscesses, bilateral frontal, temporal and sylvian empyemas and supratentorial hydrocephalus (Fig. 2). She was referred to the neurosurgical unit where drainage of abscess was done along with the insertion of ventriculoperitoneal shunt. She is being followed up regularly in the pediatric neurology and development clinic. On follow-up, she had global developmental delay, spastic quadriplegia with recurrent seizures and was started on epanutin, topiramate and baclofen together with physiotherapy. She is on gastrostomy tube feeding. No further relapse of *Salmonella* was observed in this patient.

DISCUSSION

In neonates, *Salmonella* account for a minority of confirmed cases of meningitis as compared to *Escherichia coli* and group B streptococcus^[1]. Such infections are often associated with a high complication rate, a high mortality rate and a greater potential for relapse. Although meningitis caused by non-typhoidal *Salmonella* is uncommon in economically developed countries, it is most frequent in tropical countries, particularly in infants younger than six months and is associated with higher case fatality rates than meningitis caused by other bacteria^[2,3]. Central nervous system infection is a rare complication of salmonellosis but acute neurological complication associated with *Salmonella* meningitis is commonly seen in the form of multiple cerebral abscesses.

Salmonella meningitis is associated with considerable morbidity and mortality especially in

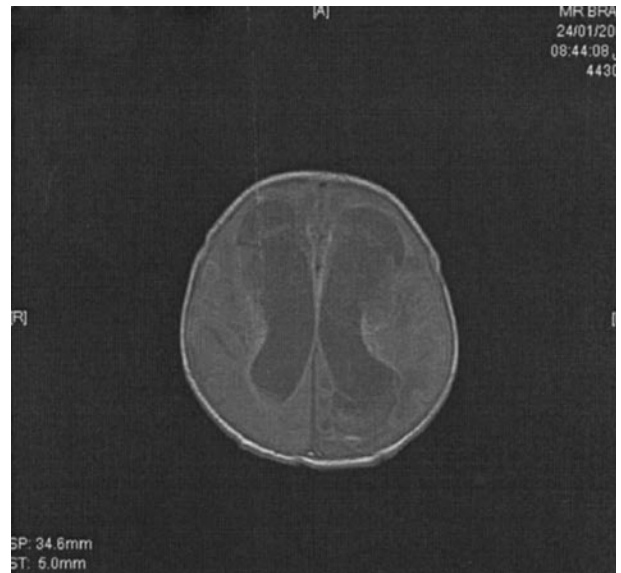


Fig. 2: MRI brain showing intraparenchymal abscesses, bilateral frontal temporal and sylvian empyemas and hydrocephalus

neonates. Neonates are at particular risk of infection because of relatively reduced gastric acidity and peristalsis. Whenever Gram-negative bacilli are seen in direct smear of CSF, possibility of *Salmonella* infection should be kept in mind and appropriate antibiotics started^[4]. Workman *et al* reported *Salmonella* enteritidis meningitis with multiple cerebral abscess in a four-week-old infant who was managed successfully with a prolonged course of antibiotics including ciprofloxacin, neurosurgical drainage and long term immunoglobulin supplements^[5].

In a study of 98 cases of extra-intestinal non-typhoidal *Salmonella* infections in children with a mean age of 2.1 years (range between newborns to 14 years) three serotypes most commonly isolated were *S. enteritidis*, *S. paratyphi* B and *S. typhimurium*^[6]. Lee *et al* reported thirteen infants aged 3 days to 9 months with *Salmonella* meningitis. The median age of onset of symptoms was four months. *Salmonella enteritidis* was the commonest serotype isolated. Nine infants developed seizures. Other complications noted were hydrocephalus, subdural effusion (four), empyema (three), ventriculitis (two), intracranial hemorrhage and cerebral abscess (one each). The presence of empyema, intracerebral abscess, ventriculitis, hydrocephalus and intracranial hemorrhage was associated with adverse neurodevelopmental sequelae or death^[7]. Our case had seizures, multiple cerebral abscesses and hydrocephalus.

Third generation cephalosporins have been used as empirical chemotherapy for meningitis caused by Gram-negative bacteria, not only because of high bactericidal activity due to low minimum inhibitory concentrations (MIC's) but also because they penetrate the blood brain barrier better than both gentamycin and chloramphenicol. The increase of resistance was

the main problem in the management of *Salmonella* infections. Ciprofloxacin has been used successfully in the treatment of *Salmonella* meningitis in neonates, given intravenously 10 mg / kg / day^[8] in two divided doses. Neuroimaging studies have been recommended for every patient with *Salmonella* meningitis^[9] in view of the high percentage of abnormalities detected. If present, a cerebral abscess will require treatment for a considerably longer period than would be given for meningitis alone. *Salmonella* is a facultative intracellular microorganism. Therefore, inadequate drug penetration may result in progress of infection. In addition, in *Salmonella* species resistance against chloramphenicol, ampicillin, cephalosporin and cotrimoxazole have been reported^[10]. Ciprofloxacin and third generation cephalosporins have been used in combination with success for prolonged periods to treat cerebral abscesses caused by *Salmonella* spp^[5,10]. Wessalowski *et al* reported a neonate with multiple brain abscesses caused by *Salmonella enteritidis*, successfully treated with ciprofloxacin^[10]. Ciprofloxacin was given to our patient also in addition to cephalosporin.

Transplacental infection of a fetus by *Salmonella enteritidis* leading to sepsis and death in a premature infant born to a mother with gastroenteritis has been reported by Roll *et al*^[11]. Nosocomial outbreaks of *Salmonella enteritidis* meningitis has been reported in a series where *Salmonella enteritidis* was isolated from seven out of twenty four children aged one day to six years, of whom five were *Salmonella enteritidis* meningitis and all the five children died^[12]. Out of the two cases of neonatal *Salmonella meningitis* reported by Hansen *et al*, one died six days after admission to hospital and the other required artificial ventilation for four days and recovered with sequelae^[13]. Multiple brain abscesses in neonate caused by *Salmonella enteritidis* successfully treated by ciprofloxacin has been reported^[8,9]. Most cases with cerebral abscess require neurosurgical intervention and early diagnosis and quick surgical evacuation leads to success^[14].

Our case presented with central nervous system complications and DIC and was treated with cefotaxime and ciprofloxacin for which the organism *Salmonella enteritidis* was sensitive. As she presented with complications she required neurosurgical intervention. In spite of the aggressive management, she recovered with sequelae.

CONCLUSION

Neonatal *Salmonella enteritidis* meningitis although rare is a potentially fatal disease with a rapidly progressive course and may lead to irreversible

neurological damage or death. Emergence of multi-drug resistant strains of *Salmonella* adds to the severity of the complications seen. Hence, an early diagnosis and use of appropriate antibiotics is essential.

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Case Report

Role of MRI in Uterus Didelphys – A Case Report

Ekinadoese Juliana Aghahowa, Muneera Al- Adwani, Venkata Mallikarjuna Sontenam
Department of Radiology, Al Jahra Hospital, Kuwait

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ABSTRACT

Mullerian duct anomalies (MDAs) occur in 0.1-3% of women. They develop from coelomic epithelium and form the definitive uterovaginal canal by lateral fusion. Different degrees of failure of this fusion results in a spectrum of uterine anomalies. We report a case of obstructed uterus didelphys with left transverse vaginal septum, ipsilateral endometriotic cyst and renal agenesis with associated spina bifida occulta of the first sacral segment. Skeletal or spinal anomalies occur in 12% of cases of mullerian

agenesis, but no such association of uterus didelphys with spina bifida occulta or any skeletal anomaly has been previously mentioned in literature. The diagnosis is usually made after menarche, but its rarity and variable clinical features may contribute to a diagnostic delay for years after menarche. The importance of MRI in detecting and determining surgically correctable forms of MDAs due to its good tissue characterization and multiplanar imaging is stressed.

KEY WORDS: MRI, mullerian, uterine anomalies

INTRODUCTION

Mullerian duct anomalies (MDA) occur in 0.1-3% of women^[1]. Simon *et al* found that in the healthy fertile population, MDAs have a prevalence of 3.2%, out of which 5% present as uterus didelphys^[2]. The mullerian ducts develop at five to six weeks gestation from coelomic epithelium and form the uterovaginal canal by lateral fusion at seven to nine weeks gestation. By eight weeks, the uterovaginal canal reaches the urogenital sinus at the mullerian tubercle, while a vaginal plate develops distally in vertical fusion. The upper two thirds of the vagina is of mullerian duct origin while the lower third originates from the urogenital sinus. Failure of lateral fusion of the mullerian ducts results in uterus didelphys which is complete duplication with two uterine horns, two cervixes and two vaginas^[1]. The association of renal agenesis with MDAs is derived from the close embryologic development of the urinary and genital systems. Li *et al* reported unilateral renal agenesis in 30% of women with MDAs and 80% of women with uterus didelphys, all of which were obstructed. Unilateral renal agenesis was detected more frequently in patients with obstructed MDAs (85.6%) than in patients with unobstructed MDAs (13.6%). In all the patients with obstructed uterus didelphys, renal agenesis was located on the same side as the obstruction^[3].

CASE HISTORY

An eighteen-year-old female virgin presented on her third day of menstruation with a history of lower abdominal pain exacerbated during her menstrual cycles and dysuria for one year. Her menstrual cycles were regular, but she was unaware of the age at which she attained menarche. She had no previous medical or surgical history. Her blood parameters were normal. Pregnancy test was negative. Abdominal examination revealed a sixteen week size tender central abdominal mass arising from the pelvis. Abdominal radiograph showed spina bifida occulta of the first sacral segment. Imaging modalities included ultrasound, CT and MRI.

A pelvic ultrasound showed a midline echogenic heterogeneous 12.4 cm x 8 cm pelvi-abdominal mass and a left ovarian cyst. CT showed two uterine bodies with fluid collection in the left uterine cavity, a left ovarian cyst and solitary right kidney. MRI abdomen and pelvis showed two divergent uterine fundi, two cervixes and two vaginas (Figs. 1-3). The distended left uterus, left cervical canal and left vagina measured 13.5 cm x 8 cm and the accumulated fluid within was hyperintense on T1WI, isointense to hyperintense on T2WI and isointense on Fat Sat T2 series, denoting hemorrhagic content. There was a left transverse septum in the lower third of the vagina. There were follicular cysts less than 2 cm in the right

Address correspondence to:

Dr Eki Aghahowa, Specialist Radiologist, Department of Radiology, Al Jahra Hospital, PO Box 1807, Jahra 01020, Kuwait. Tel: +965 -24573578, Fax: +965 - 24577198, E-mail:ekiaghahowa@hotmail.com



Fig. 1: T2 Coronal image showing two widely splayed uterine horns with distension of the left horn and left uterine body with isointense fluid content. Left ovarian cyst is also seen.

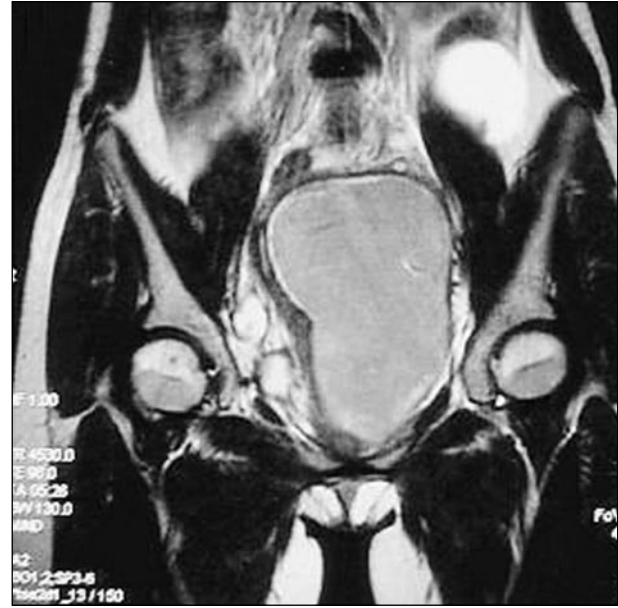


Fig. 2: T2 Coronal image showing grossly distended left vagina with isointense fluid content and left ovarian cyst



Fig. 3: T1 Coronal image showing large uterine fundal cleft

ovary. There was a 6 cm x 5 cm left ovarian cyst which was isointense to hyperintense on T1WI and showed high signal intensity on T2WI, denoting that it was a complex cyst (Fig. 4). There was also left renal agenesis. The left transverse vaginal septum was ipsilateral to the renal agenesis (Figs. 5, 6). CT could not determine the nature of the left ovarian cyst and did not detect the left transverse vaginal septum. These were only confirmed by MRI.

Surgery confirmed uterus didelphys with each separate uterus having a single fallopian tube. There was left hematometocolpos with left lower transverse vaginal septum. There was also a left endometriotic cyst.

DISCUSSION

Obstructed unilateral vagina in uterus didelphys is frequently associated with ipsilateral renal and ureter agenesis; this is known as Wunderlich-Herlyn-Werner syndrome. The syndrome is thought to be due to developmental arrest in one wolffian (mesonephric) duct that in turn affects induction of nephrogenesis and positioning of the ipsilateral paramesonephric (mullerian) duct^[4].

Although ultrasound is often the first imaging modality chosen because of its availability, short scan time, and low cost, limitations may be encountered during imaging as overlying bowel gas can confound transabdominal imaging. Transvaginal imaging, although superior to the transabdominal approach, may not always be possible, as in patients with vaginal septa. CT findings of hydro / hematometocolpos are those of a tubular, fluid filled midline mass between the bladder and the rectum. The vagina has a thin barely perceptible wall, whereas the uterus has a thicker muscular wall that enhances after IV contrast administration. However, CT causes irradiation to these women of reproductive age. MRI is considered the criterion standard for imaging uterine anomalies. MRI has consistently demonstrated 100% sensitivity and specificity for the evaluation of uterine anomalies compared to 67% specificity and 100% sensitivity for endovaginal ultrasound^[5].

The MRI appearance of hydrometrocolpos varies with the nature of uterine and vaginal contents. Serous fluid has a low signal intensity on T1WI and high signal intensity on T2WI. The signal intensity increases on T1WI if the contents are hemorrhagic^[6].



Fig. 4: T1 Coronal image showing grossly distended left vagina. The right ovarian cyst shows low signal intensity while the left endometriotic cyst is isointense.

MRI appearance of mullerian anomalies (American Fertility Society classification system)

Class I (hypoplasia / agenesis): Findings of agenesis include absence of the uterus, cervix, and / or upper two thirds of the vagina. In uterine agenesis, no identifiable uterine tissue is noted. In uterine hypoplasia, the endometrial cavity is small, with a reduced intercervical distance (< 2 cm).

Class II (unicornuate uterus): Unicornuate uterus appears banana shaped without the usual rounded fundal contour and triangular appearance of the

fundal cavity. Uterine zonal anatomy is normal.

Class III (didelphys uterus): Two separate normal-sized uteri and cervixes are seen. A septum may be visualized extending into the upper vagina. The two uterine horns are usually widely splayed and endometrial and myometrial zonal widths are preserved. Vaginal septa are most commonly associated with this type.

Class IV (bicornuate uterus): Two uterine cavities are seen with normal endometrium. The most important imaging finding is a concave fundus with a fundal cleft greater than 1 cm and an increased intercervical distance (> 4 cm) may be observed.

Class V (septate uterus): The outer fundal contour is convex, flattened, or mildly concave (fundal cleft < 1 cm). The intercervical distance is usually normal (< 4 cm) and each uterine cavity is usually small. The septum may be composed of muscle or fibrous tissue.

Class VI (arcuate uterus): MRI may detect this abnormality but, typically, it is not clinically significant because arcuate uterus has no significant negative effects on pregnancy outcome.

Class VII (DES related): MRI may detect this abnormality as a hypoplastic uterus. Typically, the DES-related anomaly is diagnosed confidently using HSG.



Fig. 5: T1 Coronal image showing distended lower left vagina and transverse septum. Right vagina is collapsed.



Fig. 6: T2 Sagittal image showing distended left vagina with transverse septum at its lower end

In uterus didelphys, the two widely spaced uterine corpora have a large fundal cleft and the intercornual angle of the divergent uterine horns is more than 75 degrees. Each horn has a fusiform shape, convex lateral margins and a central endometrial cavity surrounded by a junctional zone^[7]. In each uterus, the endometrial-myometrial width and ratio are preserved^[8]. Presence of a transverse vaginal septum leads to ipsilateral hydro or hematocolpos with reflux endometriosis^[1]. Approximately 45% of vaginal septa occur in the upper vagina, 40% in the mid vagina and 15% in the lower vagina^[9]. Didelphys uteri have the best pregnancy outcomes of all the uterine anomalies. It is believed that this may be because they have better blood flow. There is a preterm delivery rate of 24.4% and a live birth rate of 68.6%^[10].

CONCLUSION

MRI confirmed the hemorrhagic nature of the accumulated fluid in the uterus and vagina; the left transverse vaginal septum was ipsilateral to the renal agenesis and the ovarian cyst was endometriotic. Also, the association of uterus didelphys with skeletal anomaly such as spina bifida occulta which has not been previously mentioned in literature is reported. The role of MRI as a better imaging modality in detecting, diagnosing and determining surgically correctable forms of MDAs such as obstructed uterus didelphys is highlighted. There is no irradiation to the young female patient and it provides high resolution images of the female reproductive structures which

can be seen in various planes, in addition to evaluating concomitant urinary tract anomalies.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2010, 42 (1): 81 - 83

Association of Blood Levels of C-Reactive Protein with Clinical Phenotypes in Arab Schizophrenic Patients

Akanji AO, Ohaeri JU, Al-Shammri S, Fatania HR
Department of Pathology, Kuwait University Faculty of Medicine, Safat, Kuwait
E-mail: abayomi@hsc.edu.kw

Psychiatry Res 2009; 169:56-61

Schizophrenia may be associated with inflammatory reactions and C-reactive protein (CRP) is a nonspecific serum protein marker for persisting inflammatory states. This study aimed to assess concentrations of high sensitivity CRP (hsCRP) in schizophrenic Arab patients and evaluate the relationships of hsCRP levels with aspects of clinical phenotypes of the disease. Two age-matched groups of subjects were studied: (1) healthy controls, HC, n=165; (2) patients with schizophrenia, SZ: n=207. Each subject was evaluated with a standard questionnaire for age at disease onset, family history, disease severity and outcome. Serum hsCRP levels were measured by immunoassay. The two groups of subjects were similar in age, ethnic composition and socioeconomic status. Those with SZ had significantly greater serum concentrations of hsCRP. There were significant associations between hsCRP and (i) age in both groups; (ii) body mass index (BMI) in HC but not in SZ. In the latter, hsCRP levels were: (a) marginally higher in women with later age of disease onset; (ii) highest with remission and with catatonic features; and (iii) lower with family history of psychosis. The study concludes that serum levels of hsCRP are increased in clinically stable Arab patients with schizophrenia and appear related to the disorder's clinical expression. It is suggested that there may be an inflammatory component to schizophrenia which is associated with aspects of its clinical phenotype.

Active Management of Post-Renal Transplantation BK Virus Nephropathy: Preliminary Report

Halim MA, Al-Otaibi T, El-Kholy O, Gheith OA, Al-Waheeb S, Szucs G, Pacsa A, Balaha MA, Hasaneen H, Said T, Nair P, Nampoory MR
Hamed Al-Essa Organ Transplantation Centre, Ibn Sina Hospital, Safat, Kuwait
E-mail: medhatmohamed2000@yahoo.com

Transplant Proc 2009; 41:2850-2852

Objective: To assess the efficacy of leflunomide, intravenous immunoglobulins, and ciprofloxacin as active treatment of postrenal transplant BK virus nephropathy (BKVN) in graft outcome at 1 year.

Patients and methods: Renal transplant recipients with positive results of 2 BK virus polymerase chain reaction tests of urine and blood underwent graft biopsy to confirm BKVN. If BKVN was diagnosed, antimetabolite therapy (mycophenolate mofetil or azathioprine) was changed to leflunomide therapy accompanied by a course of immunoglobulin and oral ciprofloxacin.

Results: Of 18 patients evaluated, 72% were men. Nine patients received cadaveric organs, with a mean of 3.6 HLA mismatches. All patients received induction therapy (61% thymoglobulin), and 61% received antirejection therapy before BKVN was diagnosed. Maintenance immunosuppression therapy was primarily with prednisolone (94%); mycophenolate mofetil, 2 g/d (94%); and tacrolimus (61%). At baseline, mean (SD) creatinine clearance was 35.6 (11.5) mL/min/1.73(2), which decreased to 29.3 (17.3) mL/min/1.73(2) at 1 year ($P = .01$). Patients were divided into 2 groups of 9 each according to creatinine clearance values. In group 1, baseline value was 44.5 (6.6) mL/min/1.73(2), compared with 25.36 (7.8) mL/min/1.73(2) in group 2, which decreased to 42.66 (12.8) mL/min/1.73(2) ($P = .23$) and 16.76 (9.0) mL/min/1.73(2) ($P = .009$), respectively, at 1 year. Three grafts (16.7%) were lost by the end of the study, all in group 2 ($P = .03$).

Conclusion: Late diagnosis and intensive immunosuppression predispose to BKVN. Early active treatment of BKVN may improve graft outcome at 1 year posttransplantation.

Endophthalmitis after Vitrectomy and Vitrectomy Combined with Phacoemulsification: Incidence and Visual Outcomes

Wani VB, Al Sabti K, Kumar N, Mathew S, Al Kandari J, Raizada S
Al Bahar Ophthalmology Center, Kuwait city-Kuwait
E-mail: vbwani@yahoo.com

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Purpose: To study the incidence of endophthalmitis after vitrectomy and after combined vitrectomy and phacoemulsification surgery and to report the results of treatment in such cases.

Methods: This is a retrospective, noncomparative, interventional study based at a tertiary ophthalmology center in Kuwait. Cases of vitrectomy only and combined vitrectomy with phacoemulsification surgery performed during the period from January 1, 1997, to December 31, 2007, were included. Patients undergoing vitrectomy for traumatic etiologies and endophthalmitis were excluded. Patients who developed endophthalmitis after vitrectomy were identified and their records were analyzed.

Results: Six patients developed endophthalmitis among 2965 cases of all vitrectomy procedures, resulting in an incidence of 0.20%. The incidence of endophthalmitis was 0.12% for cases undergoing vitrectomy (3 out of 2564 cases) and 0.75% for cases undergoing combined vitrectomy and phacoemulsification surgery (3 out of 401 cases), respectively. Three cases were culture positive. Four cases ended up with final visual acuity of perception of hand movements or worse.

Conclusions: Incidence of endophthalmitis in our series was higher than in other studies. The visual results were poor in 4 out of 6 cases. Earlier diagnosis and more aggressive approach may be needed to improve the results of treatment in these cases.

Therapeutic Role of Low-Carbohydrate Ketogenic Diet in Diabetes

Al-Khalifa A, Mathew TC, Al-Zaid NS, Mathew E, Dashti HM
Department of Anatomy, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait

Nutrition 2009; 25:1177-1185

Introduction: Changes in dietary habits influence the glycemic level. Preliminary studies using the low-carbohydrate ketogenic diet (LCKD) were found to be quite promising in controlling diabetes mellitus. Therefore, the objectives of this study are to investigate the therapeutic effects of LCKD in experimental diabetic rats following the administration of streptozotocin (STZ).

Materials and methods: Adult rats were divided into three groups: normal diet, LCKD, and high-carbohydrate diet. Each group was subdivided into normal, sham, and diabetic groups. Diabetes was induced by a single intraperitoneal injection of STZ (55mg/kg). Specific diets were given to each group of animals for a period of 8 wk and then the animals were sacrificed. The rats were monitored daily for food and water intake, whereas body weight, urine output, and blood glucose levels were monitored weekly. The histology of the islets of Langerhans was studied by histochemical methods.

Results: The results showed that LCKD was effective in bringing blood glucose level close to normal ($P<0.01$). Food and water intake and urine output were increased in all groups except the LCKD group ($P<0.01$). The body weight was significantly reduced in all diabetic animals except in the LCKD group ($P<0.01$). Histologic studies showed significant decrease in the islet size and number of beta cells in all the diabetic groups.

Conclusion: This study indicates that LCKD has a significant beneficial effect in ameliorating the diabetic state and helping to stabilize hyperglycemia.

Correlates of Quality of Life in an Arab Schizophrenia Sample

Zahid MA, Ohaeri JU, Elshazly AS, Basiouny MA, Hamoda HM, Varghese R.

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

E-mail: zahid@hsc.edu.kw

Soc Psychiatry Psychiatr Epidemiol 2009 Sep 2 [Epub ahead of print]

Objectives: We focused on the subjective quality of life (QOL) indicators of the Lancashire quality of life profile, European version (LQoLP-EU) in a Kuwaiti schizophrenia sample. The objectives were: First, to assess the reliability and validity of the questionnaire. Second, to highlight the patients' QOL profile, in comparison with the results of the European five-nation study. Third, to examine the association of perceived needs for care, caregiver burden, service satisfaction, self-esteem and psychopathology, with three indices of global QOL: total life satisfaction or perceived QOL (PQOL) score; general wellbeing (GW) and Cantril's ladder (CL).

Method: Consecutive outpatients in stable condition and their family caregivers were interviewed with the LQoLP, and measures of needs for care, service satisfaction, caregiver burden and psychopathology.

Results: There were 130 patients (66.1% m, mean age 36.8). Majority of the patients (56%) felt satisfied with the nine domains of life investigated, and 44.6% felt "averagely" happy. Their clinical severity was moderate (BPRS-18 = 44.4). In exploratory factor analysis (FA), the original domains were mostly replicated. Reliability indices were significant (>0.7). In stepwise regression analyses, the associations of PQOL were more in number and mostly different from those of GW and CL. The correlates of PQOL included, social unmet need (8.1% of variance), staff perception of unmet need (10.3%), general satisfaction with services (11.3%), burden of caregiver supervision (3.7%), self-esteem (2.9%) and positive symptoms (2.6%). Of the nine life domains, health was the most important correlate of GW and CL, indicating the centrality of health status in judgments of subjective QOL. In secondary FA, GW and CL loaded together, but separately from life domains, implying that these are separable parts of the subjective wellbeing construct.

Conclusion: The profile of QOL scores was mostly similar to European data. The significant multivariate association with patients/staff perceptions of unmet need for care and service satisfaction indicate the usefulness of staff professional development and service improvement in outcome; and imply that promotion of QOL should be an institutional objective. Our finding about the relationship between the three global measures of QOL has added support to the emerging QOL theory.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2010; 42 (1): 84-89

VI Central American Congress on **HIV/AIDS** and Sexually Transmitted Infections (CONCASIDA)
Mar 01- 05, 2010
San Jose, *Costa Rica*
Contact: Congress Secretariat
Phone: 506-2224-2257 or 506-2234-9771;
Fax: 506-2253-7695
E-Mail: contacto@concasida2010.org or concasida2010@gmail.com

4th Middle East **Cardiovascular** Congress
Mar 03 - 05, 2010
Kish Island, *Islamic Republic of Iran*
Contact: Congress Secretariat
Phone: 0098-711-234-3529; Fax: 0098-711-234-3529
E-Mail: mecc_congress@yahoo.com

The 19th Annual International Congress of The Egyptian Society of **Gynecology and Obstetrics (ESGO)**: Advances and Debates in Clinical Obstetrics and Gynecology
Mar 03 - 05, 2010
Hurghada, *Egypt*
Contact: Mr. Alaa Abdalla or Mrs. Wala
Phone: 2-010-666-1172; Fax: 202-2402-2796
E-Mail: egyicc@link.net

30th Annual CREF: **Cardiothoracic Surgery** Symposium
Mar 04 - 07, 2010
Newport Beach, CA, *United States*
Contact: Susan Westwood
Phone: 805-541-3118; Fax: 716-809-4082
E-Mail: s.westwood@sbcglobal.net

14th World Congress of **Gynecological Endocrinology**
Mar 04 - 07, 2010
Florence, *Guyane, USA*
Contact: Congress Secretariat
Phone: 39-0-5050-1934; Fax: 39-0-5050-1239
E-Mail: isge2010registrations@biomedicaltechnologies.com

68th Annual Meeting of the American Academy of **Dermatology**
Mar 05- 09, 2010
Miami, FL, *United States*
Contact: American Academy of Dermatology
Phone: 866-503-SKIN (7546) / 847-240-1280 Fax: 847-240-1859
E-Mail: MRC@aad.org

NYSORA World **Anesthesia** Congress
Mar 07 - 12, 2010
Dubai, *United Arab Emirates*
Contact: Jo Watling
Phone: 00-441-462-441-166; Fax: 00-441-462-452-562
E-Mail: jo.watling@choicelive.com

Interventional Cardiology 2010: 25th Annual International Symposium
Mar 07- 12, 2010
Snowmass Village, CO, *United States*
Contact: Laurel Steigerwald
Phone: 760-720-2263; Fax: 760-720-6263
E-Mail: IC2010@promedicacme.com

29th Annual **Dialysis** Conference
Mar 08- 10, 2010
Houston, TX, *United States*
Contact: Office of Continuing Medical Education, University of Missouri
Phone: 573-882-4105; Fax: 573-882-5666
E-Mail: beckmannli@health.missouri.edu / Carrk@health.missouri.edu

30th International Symposium on **Intensive Care and Emergency Medicine**
Mar 09 - 12, 2010
Brussels, *Belgium*
Contact: Ms Véronique De Vlaeminck
Phone: 32-25-553-631; Fax: 32-25-554-555
E-Mail: sympicu@ulb.ac.be

ThoracicGulf 2010. Saudi Thoracic Society, American College of Chest Physicians, and Emirates Respiratory Society Joint **Pulmonary Update**
Mar 11- 13, 2010
Abu Dhabi, *United Arab Emirates*
Contact: Prof. Mohamed Al-Hajjaj Phone: 00-966-505-419-532; Fax: 0096-14-679-496
E-Mail: msalhajjaj@yahoo.com

Comprehensive **Interventional Pain Management**, CIPM - III
Mar 11- 14, 2010
Mumbai, *India*
Contact: Dr. Kailash Kothari (M.D.)
Phone: 91-22-2368-5971 or 91-986-702-7500
E-Mail: cipmindia@gmail.com

1st International (ADDC) Abu Dhabi **Diabetes** Congress
Mar 12 - 14, 2010
Abu Dhabi, *United Arab Emirates*
Contact: Congress Manager
Phone: 44-0-1-903-288-288; Fax: 44-0-1-903-520-520
E-Mail: secretariat@addc.gr

American College of **Cardiology** (ACC) 59th Annual
Scientific Session
Mar 14 - 16, 2010
City: Atlanta, GA, *United States*
Contact: Conference Secretariat
Phone: 202-375-6000 ext. 5603 or 800-253-4636 ext. 5603
E-Mail: accregistration@jpsargo.com or resource@acc.org

2010 Winter Escape **Emergency Medicine** Update
Mar 15 - 19, 2010
Terrace, BC, *Canada*
Contact: Jim Barr
Phone: 888-308-3007; Fax: 780-483-5995
E-Mail: jim@tandtadventures.com

Gulf Thoracic 2010 Saudi Thoracic Society, American
College of Chest Physicians, and Emirates Respiratory
Society Joint Update in Pulmonary Medicine
Mar 17- 20, 2010
Abu Dhabi, *United Arab Emirates*
Contact: Prof. Mohamed Al-Hajjaj
Phone: 00-966-505-419-532; Fax: 0096-14-679-496
E-Mail: msalhajjaj@yahoo.com

1st International Congress Southern European **Allergy**
Societies (SEAS)
Mar 18 - 20, 2010
Florence, *Italy*
Contact: Congress Secretariat: AIM Group Florence
Office - Viale G. Mazzini, 70 - 50132 Florence, Italy
Phone: 39-055-233-881; Fax: 39-055-248-0246
E-Mail: seas2010@aimgroup.it

7th World Congress of the International Academy of
Cosmetic Dermatology (IACD)
Mar 18 - 23, 2010
Cairo, *Egypt*
Contact: Ms Sandy Silverstein
E-Mail: IACD@IACDworld.org

2nd African Middle Eastern Congress on **Digestive**
Oncology
Mar 19- 21, 2010
Alexandria, *Egypt*
Contact: Ms. Fifi Erian
Phone: 20-224-532-916 / 20-224-532-917;
Fax: 20-224-533-515
E-Mail: alfa@alfamedical.org

Innovations in **Plastic Surgery**
Mar 19- 21, 2010
Fort Lauderdale, FL, *United States*
Contact: Diana Sheffey
Phone: 954-659-5490; Fax: 954-659-5491
E-Mail: dheffed@ccf.org

Keystone Symposia: **HIV Vaccines** (X5)
Mar 21- 24, 2010
Banff, AB, *Canada*
Contact: Keystone Symposia Meeting Organiser
Phone: 1-800-253-0685 / 1-970-262-1230;
Fax: 1-970-262-1525
E-Mail: info@kestonesymposia.org

14th Pan Arab Conference on **Diabetes** PACD14
Mar 23 - 26, 2010
Cairo, *Egypt*
Contact: Mahmoud Ibrahim, MD
Phone: 2012-213-1868; Fax: 202-2472-9793
E-Mail: mahmoud@arab-diabetes.com

1st Egyptian **Organ Transplant** Congress
Mar 24 - 26, 2010
Cairo, *Egypt*
Contact: Inji Yousef
Phone: 00-201-2214-4557; Fax: 00-202-3749-1478
E-Mail: congress@egyptianotc.org or
inji@leapfrog.com.eg

7th European **Breast Cancer** Conference
Mar 24 - 27, 2010
Barcelona, *Spain*
Contact: ECCO - the European CanCer Organisation,
Avenue E. Mounier 83, B-1200 Brussels, Belgium
Phone: 32-27-750-201
Fax: 32-27-750-200
E-Mail: adline.lewuillon@ecco-org.eu / riitta.kettunen@ecco-org.eu

41st Annual Meeting of the Society for **Paediatric**
Nephrology
Mar 25 - 27, 2010
Hamburg, *Germany*
Contact: Jutta Vach
E-Mail: jutta.vach@conventus.de

6th International Scientific Meeting of the International
Society for **Ultrasound in Obstetrics and Gynecology**
(ISUOG 2010)
Mar 25 - 28, 2010
Cairo, *Egypt*
Contact: Congress Secretariat
Phone: 202-2405-3575; Fax: 202-2402-0609
E-Mail: info@pioneer-events.com

APASL 2010 Beijing - 20th Conference of the Asian Pacific Association for the Study of the **Liver** (APASL)
Mar 25- 28, 2010
Beijing, *China*
Contact: APASL 2010 Secretariat
E-Mail: info@apasl2010beijing.org

Hair and Scalp Diseases in Clinical Practice.
International Course and Symposium
Mar 26 - 28, 2010
Warsaw, *Poland*
Contact: Lidia Rudnicka
Phone: 48-225-081-480; Fax: 48-225-081-492
E-Mail: lidiarudnicka@yahoo.com

5th European Multidisciplinary **Colorectal Cancer**
Congress 2010
Mar 28 - 30, 2012
Nice, *France*
Contact: Rob Zikkenheimer
Phone: 31-73-690-1415; Fax: 31-73-690-1417
E-Mail: r.zikkenheimer@congresscare.com

Saudi **Hypertension** Conference 2010
Mar 29 - 31, 2010
Jeddah, *Saudi Arabia*
Contact: Tawfik Albassam
Phone: 96-638-552-733; Fax: 96-638-552-733
E-Mail: info@shc2009.org

5th International Asian Pacific Organization for **Cancer Prevention** (APOCP) Conference
Apr 03 - 07, 2010
Istanbul, *Turkey*
Contact: Nejat Ozgul
Phone: 90-312-437-8900; Fax: 90-312-437-8466
E-Mail: info@apocp.net

The 14th Annual Scientific Meeting of the Egyptian **Hypertension** Society
Apr 07 - 09, 2010
Cairo, *Egypt*
Contact: Prof. Ahmed Magdy
Phone: 202-2794-8877; Fax: 202-2794-8879
E-Mail: ehs@link.net

13th World Congress on **Cancers of the Skin**
Apr 07 - 10, 2010
Madrid, *Spain*
Contact: Congress Organizer
Phone: 34-690-846-097 Fax: 34-932-057-230
E-Mail: sbc@sbc-congresos.com

8th Gulf **Heart** Association Conference
Apr 08 - 10, 2010
Doha, *Qatar*
Contact: Conference Secretariat: Gulf Heart Association
Phone: 00-974-439-3800 or 00-974-439-3802;
Fax: 00-974-444-3786
E-Mail: GHAcadio@hmc.org.qa

6th World Congress on **Diabetes and its Complications** (WCPD)
Apr 08 - 11, 2010
Dresden, *Germany*
Contact: Sylvia Neumann
Phone: 49-351-3201-7320; Fax: 49-351-3201-7333
E-Mail: sneumann@intercom.de or info@wcpd2010.com

The 3rd Congress of the Asia Pacific **Initiative on Reproduction** (ASPIRE 2010)
Apr 09 - 11, 2010
Bangkok, *Thailand*
Contact: KENES International
Phone: 41-229-080-488; Fax: 41-229-069-140
E-Mail: aspire2010@kenes.com

20th Annual Meeting of the European Society of Clinical **Microbiology and Infectious Diseases**
Apr 10 - 13, 2010
Vienna, *Austria*
Contact: European Society of Clinical Microbiology and Infectious Diseases
Phone: 41-616-867-799; Fax: 41-616-867-798
E-Mail: info@escmid.org

2010 Annual Conference of the American Society for **Laser Medicine and Surgery**
Apr 14 - 18, 2010
Phoenix, *AZ, United States*
Contact: American Society for Laser Medicine and Surgery, 2100 Stewart Avenue, Suite 240, Wausau, WI 54401
Phone: 715-845-9283; Fax: 715-848-2493
E-Mail: information@aslms.org

The 45th Annual Meeting of the European Association for the Study of the **Liver** (EASL 2010)
Apr 14 - 18, 2010
Vienna, *Austria*
Contact: Secretariat: KENES International
Phone: 41-22-807-0360
Fax: 41-22-328-0724
E-Mail: easloffice@easloffice.eu

7th Mediterranean Meeting on **Hypertension and Atherosclerosis**
Apr 14 - 18, 2010
Nevsehir, *Turkey*
Contact: Ayse Ozdilli Irgin
Phone: 90-212-347-6500; Fax: 90-212-347-6505
E-Mail: hypertension@slsturizm.com.tr

Valves in the Heart of the Big Apple VI: **Evaluation & Management of Valvular Heart Diseases** 2010
Apr 15 - 17, 2010
New York State, *NY, United States*
Contact: Leslie J. Yerman
Phone: 212-561-9879; Fax: 212-452-2027
E-Mail: info@heartvalveconference.com

59th European Society for **Cardiovascular Surgery** (ESCVS) International Congress
Apr 15 - 18, 2010
Izmir, *Turkey*
Contact: Prof. Dr. Öztekin Oto
Phone: 0232-464-19-63; Fax: 0232-464-24-70
E-Mail: info@oztekinoto.com

The Tenth International Conference of the Jordan **Cardiac Society**
Apr 20 - 22, 2010
Amman, *Jordan*
Contact: Ms. Susan
Phone: 00-962-6-553-9771; Fax: 00-962-6-551-0090
E-Mail: araborganizers@index.com.jo

2010 Annual Meeting of the American Society for **Aesthetic Plastic Surgery** (ASAPS)
Apr 22 - 28, 2010
Washington, DC, *United States*
Contact: American Society for Aesthetic Plastic Surgery (ASAPS)
Phone: 800-364-2147; Fax: 562-799-1098
E-Mail: asaps@surgery.org

American Society of Regional **Anesthesia and Pain Medicine** (ASRA) 35th Annual Regional Anesthesia Meeting and Workshops
Apr 22 - 25, 2010
Toronto, ON, *Canada*
Contact: Meeting Organiser: American Society of Regional Anesthesia and Pain Medicine
Phone: 847-825-7246 ; E-Mail: asra@asahq.org

The 12th European Congress of **Endocrinology** (ECE)
Apr 24 - 28, 2010
Prague, *Czech Republic*
Contact: Congress Secretariat
Phone: 44-0-1454-642-240 ; Fax: 44-0-1454-642-222
E-Mail: ece2010@euro-endo.org

Emirates Critical Care Conference - Dubai 2010 in conjunction with 2nd Asia Africa Conference of the World Federation of Societies of **Intensive and Critical Care Medicine** (WFSICCM)
Apr 25 - 27, 2010
Dubai, *United Arab Emirates*
Contact: Ms. Gurpreet Kaur
Phone: 00-971-4-268-9040; Fax: 00-971-4-268-9030
E-Mail: conferences@infomedevents.ae

British **Renal Society**: BRS Conference 2010
Apr 26- 29, 2010
Manchester, England, *United States*
Contact: Conference Secretariat
Phone: 44-1-483-764-114; Fax: 44-1-483-727-816
E-Mail: brs@britishrenal.org

Saudi Critical Care Society Conference and Scientific Meeting 2010
Apr 27- 29, 2010
Jeddah, *Saudi Arabia*
Contact: Dr. Yasser Mandourah
Phone: 966-1-475-8022; Fax: 966-1-475-8036
E-Mail: saudi.ssc@gmail.com

The 1st International Congress on Controversies in **Allergology and Immunology**
Apr 29 - 01, 2010
Sorrento, *Italy*
Contact: Conference Secretariat: KENES International
Phone: 41-229-080-488; Fax: 41-229-069-140
E-Mail: immuno@kenes.com

The **American Roentgen Ray Society** 110th Annual Meeting
May 02 - 07, 2010
San Diego, CA, *United States*
Contact: American Roentgen Ray Society, 44211 Slatestone Court Leesburg, VA 20176-5109 Phone: 800-438-2777 / 703-729-3353; Fax: 703-729-4839
E-Mail: education@arrs.org

The 3rd Congress of the Jordanian Society of **Endocrinology, Diabetes and Metabolism** (JSED) / the Second Joint JSED-AACE Congress / The 9th Pan Arab Congress of Endocrinology & Metabolism / ISPAD PostGraduate Seminar
May 03 - 07, 2010
Amman, *Jordan*
Contact: Congress Secretariat
Phone: 962-6-464-2501 / 2 / 3; Fax: 962-6-464-2506
E-Mail: admin1@lawrenceconferences.com

The 4th International Conference of **Biomarkers in Chronic Diseases**
May 04 - 06, 2010
Riyadh, *Saudi Arabia*
Contact: Conference Secretariat
Phone: 00-96-614-675-939; Fax: 00-96-614-675-931
E-Mail: biomarkers@ksu.edu.sa

The European Congress on **Obstetrics and Gynaecology** (EBCOG)
May 05 - 08, 2010
Antwerp, *Belgium*
Contact: Congress Secretariat
Phone: 32-9-233-8660; Fax: 32-9-233-8597
E-Mail: EBCOG2010@semico.be

7th **Metabolic Syndrome, Type II Diabetes and Atherosclerosis** Congress (MSDA)
May 12 - 16, 2010
Marrakesh, *Morocco*
Contact: Lily-Claude LEVASSEUR
Phone: 33-139-042-424; Fax: 33-139-040-741
E-Mail: msda2010@agence-plb.com

FIP World Congress of Podiatry

May 13 - 15, 2010
 Amsterdam, *Netherlands*
 Contact: Wendy van Buren
 Phone: 31-0-348-443-251
 Fax: 31-0-348-446-920
 E-Mail: fip2010@mccm.nl

Alexandria Gastro Club

May 13 - 15, 2010
 Cairo, *Egypt*
 Contact: Ms. Fifi Erian
 Phone: 20-2-2453-2916 or
 20-2-2453-2917; Fax: 20-2-2453-3515
 E-Mail: alfa@alfamedical.org

26th Iranian Congress of Radiology

May 13 - 16, 2010
 Tehran, *Islamic Republic of Iran*
 Contact: Conference Secretariat - ISR
 Phone: 0098-21-4446-2078
 Fax: 0098-21-4441-1224
 E-Mail: info@icr2010.ir

World Congress of Immunodiseases and Therapy

May 15 - 17, 2010
 Beijing, *China*
 Contact: Kayla Liu
 Phone: 0086-411-8479-9479
 Fax: 0086-411-8479-9629
 E-Mail: kayla@webbitmail.cn

14th Annual International Congress on Hematologic Malignancies

May 17- 20, 2010
 Whistler, BC, *Canada*
 Contact: Physicians' Education Resource, 3500 Maple Ave, Suite 700 Dallas, TX 75219
 Phone: 888-949-0045
 Fax: 214-367-3304
 E-Mail: info@pergrouppl.com

10th International Congress of Immunology and Allergy of Iran

May 18 - 20, 2010
 Tehran, *Islamic Republic of Iran*
 Contact: Dr. Mandana Sattari
 Phone: 982-123-872-573; Fax: 982-122-439-952
 E-Mail: info@icia2010.com

10th European Society for Pediatric Dermatology Congress (ESPD)

May 20 - 22, 2010
 Lausanne, *Switzerland*
 Contact: Congress Secretariat
 Phone: 41-223-399-571; Fax: 41-223-399-631
 E-Mail: espd2010@mci-group.com

9th Asian-Pacific Congress of Cardiovascular & Interventional Radiology (APCCVIR 2010)

Jun 01 - 04, 2010
 Seoul, *Republic of Korea*
 Contact: Secretariat - APCCVIR
 Phone: 82-2-3471-8555
 Fax: 82-2-521-8683
 E-Mail: apccvir@insession.co.kr

6th World Congress of the International Society of Physical and Rehabilitation Medicine

Jun 04 - 09, 2011
 San Juan, *Puerto Rico*
 Contact: Werner Van Cleemputte, Managing Director
 Medicongress Waalpoel 28/34, B-9960 Assenede, Belgium
 Phone: 32-0-93-443-959
 Fax: 32-0-93-444-010
 E-Mail: werner@medicongress.com

29th European Academy of Allergy and Clinical Immunology Congress (EAACI)

Jun 05 - 09, 2010
 London, England, *United Kingdom*
 Contact: Congress Secretariat
 E-Mail: eaaci2010@congrex.com

International College of Neuropsychopharmacology 2010 Congress

Jun 06 - 10, 2010
 Hong Kong, *China*
 Contact: Organiser
 Phone: 0-1-355-244-966;
 Fax: 0-1-355-249-959
 E-Mail: cinp2010@congrex.com

29th World Congress of Biomedical Laboratory Science

Jun 06 - 10, 2010
 Nairobi, *Kenya*
 Contact: Hila Vakrat
 Phone: 41-0-22-533-0948
 Fax: 41-0-22-580-2953
 E-Mail: secretariat@akmlso-ifbls2010.org

13th International Conference on Emergency Medicine

Jun 09- 12, 2010
 Singapore, *Singapore*
 Contact: Stella Chee
 Phone: 65-63-795-261; Fax: 65-64-752-077
 E-Mail: admin@icem2010.org

The 43rd Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

June 09 - 12, 2010
 Istanbul, *Turkey*
 Contact: Meeting Organiser
 Phone: 44-0-845-1800-360; Fax: 44-0-870-442-9940
 E-Mail: espghan2010@mci-group.com

Euroanaesthesia 2010: The European **Anaesthesiology** Congress
Jun 12 - 15, 2010
Helsinki, *Finland*
Contact: Secretariat
Phone: 32-0-27-433-290; Fax: 32-0-27-433-298
E-Mail: registration@euroanesthesia.org

2nd International Congress on **Metabolic Syndrome, Obesity & Diabetes**
Jun 16 - 18, 2010
Zanjan, *Islamic Republic of Iran*
Contact: Dr. Faranak Sharifi
Phone: 00-982-417-270-814; Fax: 00-982-417-270-815
E-Mail: zmdrc@zums.ac.ir

World Congress of **Cardiology**
Jun 16 - 19, 2010
Beijing, *China*
Contact: Conference Secretariat: KIE
Phone: 551-150-521-215; Fax: 551-150-520-286
E-Mail: tjioekie@uol.com.br

6th Congress of the European Association of **Dermatologic Oncology**
Jun 16 - 19, 2010
Athens, *Greece*
Contact: Mrs. Penelope Mitroyianni
Phone: 30-210-725-7693; Fax: 30-210-725-7532
E-Mail: info@eado2010.org

Cardiostim 2010 - 17th World Congress in **Cardiac Electrophysiology and Cardiac Techniques**
Jun 16 - 19, 2010
Nice, *France*
Contact: Jocelyne Toulouse
Phone: 33-01-47-56-24-56; Fax: 33-01-47-56-24-55
E-Mail: cardiostim@wanadoo.fr

16th World Congress for **Bronchology** - WCB; 16th World Congress for **Bronchoesophagology** - WCBE
Jun 20 - 23, 2010
Mannheim, *Germany*
Contact: Heike Esmann
Phone: 0049-0-89-307-1011; Fax: 0049-0-89-307-1021
E-Mail: heike.esmann@cocs.de

CARS 2010 - **Computer Assisted Radiology and Surgery** - 24th International Congress and Exhibition
Jun 23 - 26, 2010
Geneva, *Switzerland*
Contact: CARS Conference Office - Mrs. Franziska Schweikert
Phone: 49-7742-922-434; Fax: 49-7742-922-438
E-Mail: office@cars-int.org

6th Asian Interventional **Cardiovascular Therapeutics** Congress
Jul 01 - 03, 2010
Singapore, *Singapore*
Contact: Congress Secretariat
Phone: 65-6496-6845 or 65-6496-6850; Fax: 65-6496-6853
E-Mail: conferenceinfo@nhg.com.sg

Psoriasis International Network Congress 2010
Jul 01 - 04, 2010
Paris, *France*
Contact: Congress Secretariat
Phone: 33-0-153-858-259
Fax: 33-0-153-858-283
E-Mail: pso2010@mci-group.com

World Congress of the World Federation of **Hemophilia**
Jul 10 - 14, 2010
Buenos Aires, *Argentina*
Contact: Maria Milagros Salas - Congress & M Manager
Phone: 1-514-394-2837
E-Mail: hemophilia2010@wfh.org

7th International Congress on **Neuroendocrinology**
Jul 10 - 15, 2010
Rouen, *France*
Contact: Secretary General: William Rostene, INSERM U.732 Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Saint-Antoine 75012 Paris, France
Phone: 33-149-284-676
E-Mail: william.rostene@st-antoine.inserm.fr

16th World Congress of **Basic & Clinical Pharmacology**
Jul 13 - 23, 2010
Copenhagen, *Denmark*
Contact: Prof. Kim Brøsen / Tina Ludvig
E-Mail: kbrosen@health.sdu.dk / tludvig@health.sdu.dk

XVIII International **AIDS Conference** (AIDS 2010)
Jul 18 - 23, 2010
Vienna, *Austria*
Contact: International AIDS Society HQ, PO Box 20, CH - 1216 Cointrin, GENEVA, Switzerland
Phone: 41-0-22-7-100-800
Fax: 41-0-22-7-100-899
E-Mail: info@iasociety.org

15th World Congress on **Heart Disease**, Annual Scientific Sessions 2010
Jul 24 - 27, 2010
Vancouver, BC, *Canada*
Contact: Asher Kimchi, M.D.
Phone: 310-657-8777; Fax: 310-659-4781
E-Mail: klimedco@ucla.edu

WHO-Facts Sheet

1. Reducing Child Deaths from Pneumonia
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3. Millions of Premature Deaths can be Prevented by Tackling Global Health Risks
4. New HIV Recommendations to Improve Health, Reduce Infections and Save Lives
5. Road Accidents, Suicide and Maternal Conditions among Leading Causes of Death in Young People

Compiled and edited by
Babichan K Chandy

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1. REDUCING CHILD DEATHS FROM PNEUMONIA

US\$ 39 billion needed to prevent and control the world's leading killer of young children

A comprehensive action plan that can save up to 5.3 million children from dying of pneumonia by 2015 was launched in November 2009, by the WHO and United Nations Children's Fund (UNICEF).

Pneumonia is the biggest cause of child deaths in the world, killing 1.8 million children under five years of age every year, more than 98% of which occur in 68 developing countries. In spite of its huge toll, relatively few resources are dedicated to tackling this child killer.

The Global action plan for the prevention and control of pneumonia (GAPP) includes recommendations on what needs to be done, specific goals and targets, and estimates of what it will cost and how many lives will be saved. Its aim is to increase awareness of pneumonia as a major cause of child deaths, and it calls on global and national policy-makers, donor agencies and civil society to take immediate action to implement the plan.

"This action plan provides the strategy to prevent and control pneumonia, which today kills more children than any other illness," said Dr Margaret Chan, Director-General of WHO. "We know the strategy will work, and if it is applied in every high burden country, we will be able to prevent millions of deaths."

"Pneumonia is the leading cause of under-age-five mortality, killing over 4000 children every day," said UNICEF Executive Director, Ann M. Veneman.

"Effective interventions to reduce deaths caused by pneumonia must be used more widely and made more readily available for children at risk."

The release of the GAPP strategy coincides with the first Global Pneumonia Summit being held in New York City on 2 November.

The GAPP has a three-pronged vision:

- Protecting every child by providing an environment where they are at low risk of pneumonia (with exclusive breastfeeding for six months, adequate nutrition, preventing low-birth-weight, reducing indoor air pollution, and increasing hand washing);
- Preventing children from becoming ill with pneumonia (with vaccination against its causes: measles, pertussis, *Streptococcus pneumoniae* and *Haemophilus influenzae b*, as well as preventing and treating HIV in children, and providing zinc for children with diarrhoea);
- Treating children who become ill with pneumonia with the right care and antibiotics (in communities, health centres and hospitals).

The cost of implementing the GAPP by scaling up the recommended measures in the 68 high burden countries is estimated at US\$ 39 billion for 2010-2015. The costs are expected to double over the six-year period, rising from an annual need of US\$ 3.8 billion in 2010 to US\$ 8.0 billion by 2015.

Specific targets and goals to be reached by 2015 under the GAPP strategy are to expand coverage of all relevant vaccines and exclusive breastfeeding rates to 90%, and raise the level of access to appropriate

Address correspondence to:

Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: <http://www.who.int/>

pneumonia case management to 90%. This will lead to a reduction in child pneumonia deaths by 65% and cutting the number of severe pneumonia cases in children by 25%, compared to 2000 levels.

*For more information contact: Olivia Lawe-Davies,
WHO, Geneva. Tel: +41 22 791 1209; E-mail:
lawedavieso@who.int*

2. HOSPITALS MUST BE PROTECTED DURING NATURAL DISASTERS

International Day for Disaster Reduction 2009: urgent action needed to protect hospitals from natural hazards

The tragedies that struck the Asia and Pacific region lately underscore that urgent action must be taken to better protect hospitals from natural disasters. Large-scale human suffering is exacerbated when the very services that are most needed to save lives - hospitals, clinics and other health facilities - are counted among the casualties.

Dozens of hospitals and health facilities each year are themselves impacted by floods, hurricanes, cyclones, earthquakes and other natural hazards because safety measures were not integrated in their design, location or construction.

Campaign ensures access to health facilities after natural hazards

The Hospitals safe from disasters theme was also used for the 2008-09 World Disaster Reduction campaign that culminated in October 2009. This two-year campaign has been a joint initiative of ISDR, WHO and the World Bank aimed at ensuring people's access to functioning health facilities during and after natural hazards. The ISDR highlighted the gains made during the campaign and the work that still needs to be done in making hospitals safer from disasters.

"Since the beginning of the campaign, much has been achieved to make hospitals safer but more investments are still needed to improve the functionality of hospital when disasters occur," says Margareta Wahlström, Special Representative of the UN Secretary-General for Disaster Risk Reduction. According to a recent WHO survey, only 50% of all country's health sectors have a budget allocation for risk reduction and emergency preparedness.

Hospitals and health facilities are in the frontline when floods, hurricanes, cyclones, and earthquakes strike and many are adversely impacted because safety measures were not integrated in their design, construction and functionality. There are at least 90,000 hospitals and other health facilities in the world's 49 least-developed countries, many of which are vulnerable to disasters, including those related to the harmful effects of climate change.

Safety of health facilities must be ensured

"No new hospital should be built unless it can withstand the impact of natural hazards," Ms Wahlström adds. "Existing health facilities should also be assessed for their safety and action take to improve their safety and the level of their preparedness."

Several countries in Latin America and the Caribbean have already assessed the safety of their health facilities and set priorities for making improvements. Mexico has demonstrated that it is possible to make hospitals safer by applying a hospital safety index to more than 1000 of its high-risk facilities. The hospital safety index measures 145 crucial spots in hospitals that will allow their safety classification according to three main levels.

The hospital safety index has now been applied to many facilities in Bolivia, Ecuador and Peru and in countries elsewhere in the world, such as Oman, Sudan and Tajikistan. Dubai, within the United Arab Emirates has also committed to assessing half of its hospitals by 2010 and the remainder by the end of 2011. Hundreds of health professionals worldwide have been trained in emergency preparedness.

WHO will continue working with governments to achieve the objectives of the campaign and assure that they remain a priority for governments together with financial institutions, private and non-government organizations, professional bodies, health institutions and workforce, and international agencies.

Preparedness reduces risk

The campaign has also led to the launch in London, hosted by the UK Health Protection Agency, of an international thematic platform on disaster risk reduction for health, which will facilitate action from international and national partners on reducing deaths, injuries and illness from emergencies, disasters and other crises.

"Preparedness and risk reduction is the way ahead in health and humanitarian action. By working together, countries and communities can deal with these risks, particularly by reducing vulnerabilities and building capacities to mitigate and respond to all emergencies they may face," said Dr Eric Laroche, WHO's Assistant Director-General for Health Action in Crises.

The last global platform for disaster risk reduction held in Geneva proposed that by 2011 national assessments of the safety of existing health facilities should be undertaken, and that by 2015 concrete action plans for safer hospitals should be developed and implemented in all disaster prone countries. Hospital safety will remain one of the main elements of the new UNISDR campaign on cities at risk that will be launched next year.

The Hospital Safety Index was developed through a lengthy process of dialogue, testing and revision, over a period of two years, initially by the Pan American Health Organization's Disaster Mitigation Advisory Group (DiMAG) and later with input from other specialists in Latin America and the Caribbean.

*For more information, contact: Paul Garwood,
Communication Officer, Health Action in Crises,
WHO, Geneva. Mobile: +41 79 475 5546;
Email: garwoodp@who.int*

3. MILLIONS OF PREMATURE DEATHS CAN BE PREVENTED BY TACKLING GLOBAL HEALTH RISKS

Global life expectancy could be increased by nearly five years by addressing five factors affecting health – childhood underweight, unsafe sex, alcohol use, lack of safe water, sanitation and hygiene, and high blood pressure, according to a report published by WHO in October 2009.

These are responsible for one-quarter of the 60 million deaths estimated to occur annually.

Global Health Risks describes 24 factors affecting health. These are mixture of environmental, behavioural and physiological factors, such as air pollution, tobacco use and poor nutrition.

The report also draws attention to the combined effect of multiple risk factors. Many deaths and diseases are caused by more than one risk factor and may be prevented by reducing any of the risk factors responsible for them.

"More than a third of the global child deaths can be attributed to a few nutritional risk factors such as childhood underweight, inadequate breastfeeding and zinc deficiency," says Colin Mathers, Coordinator for Mortality and Burden of Disease at WHO.

Eight risk factors alone account for over 75% of cases of coronary heart disease, the leading cause of death worldwide. These are alcohol consumption, high blood glucose, tobacco use, high blood pressure, high body mass index, high cholesterol, low fruit and vegetable intake and physical inactivity. Most of these deaths occur in developing countries.

"Understanding the relative importance of health risk factors helps governments to figure out which health policies they want to pursue," says Mathers. "In many countries there is a complex mix of risk factors. Countries can combine this type of evidence along with information about policies and their costs to decide how to set their health agenda."

Other findings:

- nine environmental and behavioural risks, together with seven infectious causes, are responsible for 45% of cancer deaths worldwide;

- worldwide, overweight and obesity causes more deaths than underweight;
- unhealthy and unsafe environments cause one in four child deaths worldwide;
- 71% of lung cancer deaths are caused by tobacco smoking;
- in low-income countries, easily remedied nutritional deficiencies prevent one in 38 newborns from reaching the age of five;
- 10 leading preventable risks decrease life expectancy by nearly seven years globally and by more than 10 years for the region of Africa.

The report uses extensive data from WHO and other scientific studies. It estimates the effects of 24 risks to health on deaths, diseases and injuries by region, age, sex and country income for the year 2004. These are the most recent data available due to the time required for collection and analysis.

*For more information contact: Alice Ghent,
Communications Officer. Tel.: +41 22 791 1498; Mobile:
+41 79 206 1087; Email: ghenta@who.int*

4. NEW HIV RECOMMENDATIONS TO IMPROVE HEALTH, REDUCE INFECTIONS AND SAVE LIVES

On the eve of World AIDS Day, the World Health Organization (WHO) released (30th November) new recommendations on treatment, prevention and infant feeding in the context of HIV, based on the latest scientific evidence.

WHO now recommends earlier initiation of antiretroviral therapy (ART) for adults and adolescents, the delivery of more patient-friendly antiretroviral drugs (ARVs), and prolonged use of ARVs to reduce the risk of mother-to-child transmission of HIV. For the first time, WHO recommends that HIV-positive mothers or their infants take ARVs while breastfeeding to prevent HIV transmission.

"These new recommendations are based on the most up to date, available data," said Dr Hiroki Nakatani, Assistant Director General for HIV / AIDS, TB, Malaria and Neglected Tropical Diseases at the World Health Organization. "Their widespread adoption will enable many more people in high-burden areas to live longer and healthier lives." An estimated 33.4 million people are living with HIV / AIDS, and there are some 2.7 million new infections each year. Globally, HIV / AIDS is the leading cause of mortality among women of reproductive age.

New treatment recommendations

In 2006, WHO recommended that all patients start ART when their CD4 count (a measure of immune

system strength) falls to 200 cells/mm³ or lower, at which point they typically show symptoms of HIV disease. Since then, studies and trials have clearly demonstrated that starting ART earlier reduces rates of death and disease. WHO is now recommending that ART be initiated at a higher CD4 threshold of 350 cells/mm³ for all HIV-positive patients, including pregnant women, regardless of symptoms.

WHO also recommends that countries phase out the use of Stavudine, or d4T, because of its long-term, irreversible side-effects. Stavudine is still widely used in first-line therapy in developing countries due to its low cost and widespread availability. Zidovudine (AZT) or Tenofovir (TDF) are recommended as less toxic and equally effective alternatives.

The 2009 recommendations outline an expanded role for laboratory monitoring to improve the quality of HIV treatment and care. They recommend greater access to CD4 testing and the use of viral load monitoring when necessary. However, access to ART must not be denied if these monitoring tests are not available.

Preventing mother-to-child transmission and improving child survival

In 2006, WHO recommended that ARVs be provided to HIV-positive pregnant women in the third trimester (beginning at 28 weeks) to prevent mother-to-child transmission of HIV. At the time, there was insufficient evidence on the protective effect of ARVs during breastfeeding. Since then, several clinical trials have shown the efficacy of ARVs in preventing transmission to the infant while breastfeeding. The 2009 recommendations promote the use of ARVs earlier in pregnancy, starting at 14 weeks and continuing through the end of the breastfeeding period.

WHO now recommends that breastfeeding continue until the infant is 12 months of age, provided the HIV-positive mother or baby is taking ARVs during that period. This will reduce the risk of HIV transmission and improve the infant's chance of survival.

"In the new recommendations, we are sending a clear message that breastfeeding is a good option for every baby, even those with HIV-positive mothers, when they have access to ARVs," said Daisy Mafubelu, WHO's Assistant Director General for Family and Community Health.

National health authorities are encouraged by WHO to identify the most appropriate infant feeding practice (either breastfeeding with ARVs or the use of infant formula) for their communities. The selected practice should then be promoted as the single standard of care.

Benefits and challenges

An earlier start to antiretroviral treatment boosts the immune system and reduces the risks of HIV-

related death and disease. It also lowers the risk of HIV and TB transmission.

The new prevention of mother to child transmission (PMTCT)

recommendations have the potential to reduce mother-to-child HIV transmission risk to 5% or lower. Combined with improved infant feeding practices, the recommendations can help to improve child survival.

The main challenge lies in increasing the availability of treatment in resource-limited countries. The expansion of ART and PMTCT services is currently hindered by weak infrastructure, limited human and financial resources, and poor integration of HIV-specific interventions within broader maternal and child health services.

The recommendations, if adopted, will result in a greater number of people needing treatment. The associated costs of earlier treatment may be offset by decreased hospital costs, increased productivity due to fewer sick days, fewer children orphaned by AIDS and a drop in HIV infections.

Another challenge lies in encouraging more people to receive voluntary HIV testing and counselling before they have symptoms. Currently, many HIV-positive people are waiting too long to seek treatment, usually when their CD4 count falls below 200 cells/mm³. However, the benefits of earlier treatment may also encourage more people to undergo HIV testing and counselling and learn their HIV status.

WHO, in collaboration with key partners, will provide technical support to countries to adapt, adopt and implement the revised guidelines. Implemented at a wide scale, WHO's new recommendations will improve the health of people living with HIV, reduce the number of new HIV infections and save lives.

For more information contact: Saira Stewart, HIV/AIDS Department, Tel: +41 22 791 2511, Mobile: +41 79 467 2013; Email: stewarts@who.int

5. ROAD ACCIDENTS, SUICIDE AND MATERNAL CONDITIONS AMONG LEADING CAUSES OF DEATH IN YOUNG PEOPLE

WHO supported study of global and regional patterns of mortality in young people shows 2.6 million young people die every year

The first study of global patterns of death among people aged between 10-24 years of age has found that road traffic accidents, complications during pregnancy and child birth, suicide, violence, HIV/AIDS and tuberculosis (TB) are the major causes of mortality. Most causes of death of young people are preventable and treatable. The study, which was supported by the World Health Organization (WHO) and published

in The Lancet medical journal, found that 2.6 million young people are dying each year, with 97% of these deaths taking place in low- and middle-income countries.

There are more young people in the world today than ever before - 1.8 billion, accounting for 30% of the world's population. Until now, there has been very little information available on the causes of death among young people globally and by region. This study is intended to inform the development of policies and programmes to ensure that they improve the lives, and prevent the deaths, of young people.

Daisy Mafubelu, WHO's Assistant Director-General for Family and Community Health, said: "Young people are transitioning from childhood to adulthood - at the threshold of becoming productive members of society - yet they often fall through the cracks. It is clear from these findings that considerable investment is needed - not only from the health sector, but also from sectors including education, welfare, transport, and justice - to improve access to information and services, and help young people avoid risky behaviours that can lead to death."

WHO recommends the following interventions to promote safe behaviours, improve health and prevent deaths among young people:

- Road traffic accidents can be prevented through speed management (for example, creating low-speed zones in urban settings, setting speed limits according to road type); strictly enforcing drink-
- driving laws that limit blood alcohol concentration to 0.05 g/dl with lower limits for young or novice drivers); increasing the wearing of good quality helmets, and increasing the use of seat-belts.
- Sexual and reproductive health can be improved by ensuring that young people receive sexuality education, have access to condoms and other contraceptives, safe abortion to the full extent of the law, antenatal and obstetric care, HIV testing and counselling, and HIV/AIDS care and treatment.
- Violence and suicide can be prevented by ensuring that young people have access to life skills training; promoting positive parental involvement in the lives of young people, reducing the use of alcohol by young people, and reducing their access to lethal means (including firearms, knives, pesticides and sedatives).
- The immediate and long-term consequences of injuries and violence can be significantly reduced by improving access to effective community-level care and emergency medical care, and providing treatment and support for young people exposed to child abuse, youth violence, and sexual assault.

For more information contact: Olivia Lawe-Davies, Communications Officer, Department of Child and Adolescent Health and Development, World Health Organization, Tel. Office: +41-22-791-1209, Mobile: +41-794-755-545. Email: lawedavieso@who.int