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Editorial

Specialist Training in Endocrinology for Sri Lanka: a pragmatic approach


The medical specialty of endocrinology embraces an evidence-based, rational and cost-effective approach to the diagnosis and long-term management of a wide variety of hormonal disorders of deficiency or excess. Early diagnosis and optimal treatment of these diseases are guided by biochemical tests to a far greater extent than in most specialties. Many endocrine abnormalities are confirmed by dynamic testing that involves chemical stimulation or inhibition that often involves drug injection and a series of biochemical tests. Blood, urine and/or saliva requires multiple sampling to assess the changes of the target hormone or metabolite, based on a thorough understanding of the normal physiological processes that is controlled by the negative feedback homeostasis. An endocrinologist therefore requires being confident in knowledge and skill on the biochemical basis of hormonal imbalance, with a proper understanding of the uses and limitations of each of these classic investigations. In parallel, diagnostic imaging of the endocrine “glands” helps to localize the causative pathology, which has now advanced considerably to involve ultrasound, high resolution CT scanning and MRI that can also be coupled with isotopes and dynamic chemical tests. Another dimension of clinical endocrinology is to differentiate subclinical disease from biologic variation of growth, development and physiological changes. Atypical pattern of physical growth, development and sexual maturation requires an astute clinical approach with biochemical and other relevant testing in order to determine between the fine line of disease or normal variation.

Hence, an endocrinologist is in an excellent position to care for the person as well as the disease that often requires a life course approach, and also needs to address the genetic basis of disease along with environmental influences. Most endocrine disorders are chronic and need lifelong care. Chief amongst them are diabetes and prediabetes, which can be detected in their subclinical stage and be pre-empted by appropriate non pharmacologic and pharmacologic interventions. Additionally these conditions require an emphasis on self-care through proper patient education and empowerment. This therefore requires dedication to a holistic outlook to care through a multi-disciplinary approach, with an emphasis on behavioral change communication; where the patient and family require appropriate psycho-social inputs. Therefore the practice of clinical endocrinology personifies the need to connect a sound understanding of the cellular and molecular basis of disease with an excellent doctor-patient relationship that have an important bearing on the disease outcomes.

Sri Lanka has a rapidly ageing population and an exponential rise in non communicable diseases that includes diabetes mellitus, cardiovascular disease, cancers, thyroid disease and musculoskeletal disease along with osteoporosis. These transitions therefore require an assessment of the human resource and technical inputs required within the context of a state health system that is committed to a free service with equity. Whilst a strong and capable primary health care system is a priority in coping with these emerging health needs of chronic disease, the availability of capable specialists in the relevant subject areas would ensure quality standards of care with reduced complications, disability and premature mortality. No doubt endocrinology is a very relevant sub-specialty.

Since the turn of the millennium, the Board of Study in Medicine of the Postgraduate Institute of Medicine, Sri Lanka has been committed to the development of Endocrinology as a sub-specialty, for candidates who obtained the MD in Internal Medicine degree. The specialty training curriculum, from its infancy, encouraged and emphasized a clinical training rotation with differing trainers, sub-topics and settings; recognized research and publications and included a pre-board certification viva voce examination. In the ensuing years, the specialty board was encouraged to re-visit the evaluation process with a greater emphasis on objectivity. This resulted in a review of the UK, USA and Australian based specialty training and evaluation of Endocrinology and much discussion among trainers and trainees. A structured training schedule was developed that incorporates a continuous assessment of knowledge, skills and attitudes by a panel of trainers; each session followed by feedback to the trainee on the quality of his/her performance and suggestions for improvement. Additionally, OSCEs, MCQs with case book and log book based viva voce are conducted pre-board certification. Regular CME programmes are also conducted by the Endocrine Society and Ceylon College of Physicians.

The trainer-trainee workload is quite considerable, with regular evaluation and feedback required amidst a high clinical workload, limited resources, staff shortage
Editorial

with trainers often required to multi-task. Sub-optimal laboratory and radiology services often fail to fulfill standard endocrine testing with similar setbacks in cost effective pharmaceutical needs. It is noteworthy that several procedures, chemical tests, imaging techniques and treatment supports are lacking even in the tertiary referral teaching centres. Such setbacks in the already overstrained state health system often remain unrecognized as an important training need. Hence exposure to a state of the art training setting is still required through overseas postgraduate training prior to board certification – the arrangement which, once again, falls under the responsibilities of the trainer-trainee groups.

We therefore need to take a pragmatic approach to higher specialist training, the required supports and evaluation methods in the sub-specialty of Endocrinology, with realistic projections to ensure that state sector board certified endocrinologists will be located country-wide; initially at least on a district basis. No doubt an enabling environment must be ensured for quality training and clinical care. Continuing medical education, clinical audit, research and development, quality and safety, and appraisal of recent advances in the subject must be ensured. Multi-professional approach to diagnosis and treatment is another basic obligation that would encourage the attainment of high standards and safety of clinical care and training.

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Chandrika N Wijeyaratne
Professorial Unit, De Soysa Hospital for Women, Colombo 08 and Chairperson, Specialty Board in Endocrinology, Postgraduate Institute of Medicine, University of Colombo, Sri Lanka.
Effectiveness of screening for diabetic retinopathy by non-specialist doctors: the importance of physician-ophthalmologist collaboration in the prevention of blindness.

Sri Lanka Young Diabetes Study (SLYDS)

N P Wijesinghe¹, M Jayaweera², W M U AWijetunga², H A Dissanayake², D RMatthews², S Pathirana¹, P Katulanda²,³


Abstract

Introduction: Diabetes retinopathy (DR) is the fourth leading cause for blindness worldwide. Screening is vital for its early detection and prevention of blindness. However screening all diabetic patients by specialists is impossible, particularly in resource poor settings such as Sri Lanka. We aimed to compare the agreement between non-specialist doctors and specialist ophthalmologists in diagnosing DR and planning follow up.

Methods: A descriptive study was conducted with a cohort of patients randomly recruited from the Sri Lanka Young Diabetes Study (SLYDS). They were examined by a group of non-specialist doctors by direct ophthalmoscopy after mydriasis, and specialists (by slit lamp biomicroscopy) who were blinded to non-specialist doctors’ finding. Agreement between DR grading according to International Clinical Diabetic Retinopathy Disease Severity Scale, and follow up decisions, by non-specialist and specialist doctors were assessed with kappa statistic, using SPSS-16.

Results: Our study included 658 participants (males 36%, mean age 37.1 years, mean duration of diabetes 5.22 years (± 4.04), mean HbA1c 8.1% (±2.04)) and 123 (18.7%) had diabetes retinopathy and 54 (8.3%) required early referral. Exact agreement between ophthalmologists and non specialist doctors in determining absence or presence of diabetes retinopathy was 0.82 (Kappa 0.48, p < 0.001) while the agreement in diagnosing the grade of retinopathy was 0.76 (Kappa 0.347, p < 0.001). Junior doctors detected DR with a sensitivity and specificity of 0.68 and 0.86 respectively. Exact agreement on follow up decision was 0.92 (Kappa 0.48, p < 0.001), with 0.52 sensitivity and 0.96 specificity in decision for early referral.

Conclusion: Non-specialist doctors can identify DR with reasonable sensitivity. This should be encouraged in primary care, particularly in resource poor settings. Referring patients with any form of DR to a specialist should be recommended to prevent those with severe degrees of retinopathy from being missed for appropriate specialist care.

Introduction

According to the estimates of the International Diabetes Federation (IDF) 371 million people are affected by diabetes worldwide and 70 million of these live in the South East Asian region (1). Diabetes mellitus is the fourth leading cause of blindness in the world (2). There are approximately 93 million people with diabetic retinopathy (DR), 17 million with proliferative DR, 21 million with diabetic macular edema, and 28 million with vision threatening DR worldwide (3). The problem is expected to become worse due to the exponential increase of diabetes mellitus especially in the resource-limited nations such as Sri Lanka and India (4,5) in the South East Asian region, where 1 in 5 would have either diabetes or prediabetes. (1). The most frequent ocular complication of diabetes mellitus is diabetic retinopathy. The IDF estimates that there will be 552 million people with diabetes in the world by the year 2030 (1). Hence diabetic retinopathy will have

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the potential to become the leading cause of blindness and a serious public health problem.

Diabetic retinopathy is virtually symptomless until significant irreversible visual loss occurs. Strict glycaemic control has been shown to be effective in preventing retinopathy in a significant proportion of people with diabetes (6,7). However, retinopathy still occurs in another significant proportion with time. Early detection by screening and effective secondary prevention strategies such as laser photocoagulation and newer treatments including intra vitreal anti Vascular Endothelial Growth Factor (VEGF) are known to reduce the risk of blindness or severe visual impairment (8). Many studies have demonstrated the benefit of screening and treatment of diabetic retinopathy and its cost effectiveness both in type 1 and type 2 diabetes (9-12). A study by Javitt et al showed that by appropriate care, more than 79,000 person-years of sight would be saved (9).

Screening for diabetic retinopathy can be performed by retinal photography, direct and/or indirect ophthalmoscopic examination (13). Retinal photography is costly and available only in a very limited number of centers in Sri Lanka and other developing countries (14). Even after photography, experienced graders are needed for proper grading of diabetic retinopathy. In addition there is a serious mismatch between the number of patients and the number of health care workers trained to evaluate and treat the disorder. According to the latest prevalence estimates Sri Lanka has about 2 million patients with diabetes (3). Accordingly ophthalmologist to diabetic patient ratio is about 1:3000. Hence it is not practical for every diabetic patient to be examined by a specialist in Sri Lanka. The situation is same or even worse in many other developing countries.

If screening for retinopathy can be undertaken by non-specialist junior doctors such as house officers, senior house officers, district medical officers, and general practitioners at primary care level with acceptable sensitivity and specificity to identify those who need further care by specialists, it will make a tremendous impact on the care of diabetic patients in resource poor countries including Sri Lanka.

The objective of this study was to determine whether non-specialist doctors can screen diabetic patients for retinopathy with acceptable sensitivity and specificity and whether such doctors can reliably identify patients who need further specialist assessment and intervention.

Methods

The study was carried out in the Diabetes Research Unit, Department of Clinical Medicine, Faculty of Medicine, University of Colombo and the National Eye Hospital, Colombo. Diabetic subjects with the age at diagnosis between 16 to 40 years of age, who were recruited to the Sri Lanka Young Diabetic Study (SLYDS) were absorbed to this study after informed written consent. Patients with a history of glaucoma, dense cataract or corneal opacities were excluded, as it was difficult to perform retinal screening by non-specialist doctors.

Each patient was examined in duplicate by a team of junior medical graduates without specialized experience in ophthalmology and by a specialist team comprising a specialist and a specialist registrar. The junior medical graduates were trained in the detection of different categories of diabetic retinopathy and decision-making in a single day session.

All recruited subjects had their pupils dilated with mydriatic drops (tropicamide 1%) and were screened by the junior medical graduates by direct ophthalmoscopy. The findings were documented in a standard data sheet according to International Clinical Diabetic Retinopathy Disease Severity Scale (13) (normal, mild NPDR, Moderate NPDR, severe NPDR, proliferative DR and clinically significant macular edema). The level of the retinopathy was based on the findings of the more severely affected eye. At the end of the examination the examiner had to determine whether the subject could be followed up in the regular diabetes clinic, whether he or she needed early or urgent ophthalmic referral. The subjects with no retinopathy or mild non-proliferative retinopathy (NPDR) were considered for routine follow up, those with moderate or severe non-proliferative retinopathy with or without maculopathy were considered for early ophthalmological referral and the subjects with retinal detachment, vitreous haemorrhage or proliferative diabetic retinopathy were considered for urgent ophthalmological referral. This decision was indicated in the data sheet.

All these patients were reexamined on the same day within one or two hours by the specialist team at the National Eye Hospital, Colombo (situated at a separate location within walking distance) by indirect ophthalmoscopic examination using slit lamp biomicroscopy. The specialist team was blinded to the findings of the non-specialists. These findings and the decision about further course of action were recorded in a separate identical data sheet.

The final diagnosis of diabetic retinopathy level for each patient was made upon the findings of the specialist (ophthalmology) on the more severely affected eye. The competence of junior doctors in detecting retinopathy and making a decision for further course of action was compared with that of the specialists’ findings and decisions. The control of diabetes in this group of patients was assessed by investigating them for HbA1c. The data of patients were analyzed using SPSS version 16 and the agreement was assessed using the kappa statistic.
Comparison of screening for diabetic retinopathy by non-specialists and specialists

Results

The total number of patients was 658. The mean HbA1c was 8.10% (± 2.04), which indicated that the control of diabetes was not satisfactory. There were 123 patients (18.7%) with any degree of diabetic retinopathy. Overall 55 (8.3%) needed early referral.

The demographic characteristics of the patients are shown in Table 1.

When the findings were analyzed according to the presence or absence of diabetic retinopathy disregarding the degree of retinopathy, the agreement of any degree of diabetic retinopathy was 82.4% between the non-specialist junior doctor and the specialist team; kappa 0.48 (p<0.001) (Table 2). In 77 (11.7%), the junior doctors over diagnosed and in 39 (5.9%) under diagnosed diabetic retinopathy. The sensitivity for detecting diabetes retinopathy by the junior doctors was 0.68 and the specificity was 0.86.

In contrast to the presence of any degree of diabetic retinopathy as shown above, the exact agreement in the diagnosis of different types of diabetic retinopathy between ophthalmologists and junior doctor was 0.76, kappa 0.347.

The exact agreement on the decision for further follow up action of the subjects between the ophthalmologist and junior doctor was 0.92, kappa 0.48 (p<0.001). The sensitivity of picking up cases for early referral to ophthalmologist by the junior doctor was 0.52 and the specificity 0.96 (Table 4). Out of the 54 patients who needed early referral 26 had been missed and 26 of the 599 patients who really needed regular follow-up has been decided for early referral by the non-specialist doctor.

Table 1. Demographic characteristics of the patients

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>658</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>246 (36.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>437 (64.0%)</td>
</tr>
<tr>
<td>Average age</td>
<td>37.1 years</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>5.22 years (± 4.04)</td>
</tr>
<tr>
<td>Prevalence of diabetic retinopathy</td>
<td>123 (18.7%)</td>
</tr>
</tbody>
</table>

Table 2. Agreement on presence of diabetic retinopathy by ophthalmologist and junior doctor

<table>
<thead>
<tr>
<th>Retinopathy according to Specialist</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>84</td>
<td>77</td>
<td>161</td>
</tr>
<tr>
<td>Present</td>
<td>39</td>
<td>458</td>
<td>497</td>
</tr>
<tr>
<td>Absent</td>
<td>2</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
<td>535</td>
<td>658</td>
</tr>
</tbody>
</table>

Exact agreement: 0.82; Kappa: 0.48 (p< 0.001)

Table 3. The agreement of different types of diabetic retinopathy on fundus examination by ophthalmologist and non-specialist doctor

<table>
<thead>
<tr>
<th>Examination findings of non-specialist doctor</th>
<th>Normal</th>
<th>Mild NPDR</th>
<th>Moderate NPDR</th>
<th>Severe NPDR</th>
<th>PDR</th>
<th>CSME</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>458</td>
<td>33</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>497</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>72</td>
<td>31</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>128</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>3</td>
<td>4</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>PDR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CSME</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>535</td>
<td>70</td>
<td>40</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>658</td>
</tr>
</tbody>
</table>

Exact agreement: 0.76; Kappa: 0.347 (p< 0.001)
It is well established that screening and early treatment of diabetic retinopathy help prevent blindness. However, the diagnosis is often established late. The purpose of this study was to determine whether non-specialist doctors in primary and secondary care (house officers, senior house officers and general practitioners) can screen diabetic patients for retinopathy with acceptable sensitivity and specificity and to determine whether such doctors can reliably identify patients who need further specialist assessment for intervention.

In this study we demonstrated that eye screening by pupillary dilatation could be practically performed with ease by non-specialist practitioners. There is a reasonably high degree of agreement of the examination findings with an acceptable sensitivity (68%) and specificity (86%) for detection of the presence of diabetic retinopathy. The exact agreement was 82%. The kappa statistic was 0.48 which showed a moderate agreement.

Under diagnosis or non-diagnosis of relatively severe degrees of diabetic retinopathy was high (CSME 83.3%, severe NPDR 100%, moderate NPDR 57.5%). Out of the 12 patients with either CSME or severe NPDR, the junior doctors missed 09, which was unacceptable. The rate of under diagnosis or non-diagnosis of mild NPDR was 47.1%, which was better compared with the severe degrees of diabetic retinopathy. The exact agreement was 76%. The kappa statistic was 0.35, which showed a fair agreement.

The decision-making capability for further action after screening by the non-specialist doctors had high agreement (92%) and specificity (0.96) although the sensitivity (0.52) was low. A considerable 26/54 (48%) percentage of subjects who needed early referral were not correctly identified. The kappa statistic was 0.48, which showed a moderate agreement.

It is evident from the results that the specificity of diagnosing any form of diabetic retinopathy, identifying the exact degree of diabetic retinopathy and the action by the junior doctors was consistently high while the sensitivity was relatively low. So the junior doctors had tended to under diagnose rather than over diagnose which will lead to patients not getting the optimum treatment that they deserve.

Although junior doctors can be used to screen diabetic patients for retinopathy, they should be instructed to make an early referral to the ophthalmologist regardless of the degree of retinopathy when they detect any form of diabetic retinopathy. In this way it would be possible to minimize missing of severe degrees of retinopathy. This method will ensure that most if not all diabetics will get their eyes screened for diabetic retinopathy while enabling patients with mild, moderate and severe degrees of diabetic retinopathy to get specialist care. This will also enable ophthalmologists to render their services to the patients who really need it.

There are several limitations that must be considered in interpreting the results of this study. Firstly the training provided for the non-specialist doctors was very brief and their feedback was not obtained. Secondly the number of patients with advanced degrees of diabetic retinopathy was low.

**Conclusion**

Currently, many diabetic patients do not get screened adequately for retinopathy due to two main reasons; the lack of competent specialists especially in the rural areas of the developing countries and routine examination of the fundus by primary care physicians without dilating the pupil. Our study suggests that this can be easily performed in the primary care setting with reasonable accuracy and efficiency and a non-specialist doctor can reliably identify patients who need further specialist assessment for intervention.

Table 4. Agreement on the follow up plan by ophthalmologist and non-specialists

<table>
<thead>
<tr>
<th>Follow up plan by Specialist</th>
<th>Regular follow up</th>
<th>Early referral</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up plan by non-specialists</td>
<td>Regular follow up</td>
<td>573</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Early referral</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>599</td>
<td>54</td>
</tr>
</tbody>
</table>

Exact agreement: 0.92, Sensitivity: 0.52, Specificity: 0.96, Kappa: 0.48 (p< 0.001)
Acknowledgement

The authors would like to thank the staff of the retinal unit, room number 1 and 2 of the National Eye Hospital, Colombo, the staff of the Diabetes Research Unit of the Faculty of Medicine of the University of Colombo for their support and all subjects who participated in the study. Funding for this study was provided from the Oxford Centre for Diabetes Endocrinology and Metabolism.

References
Diabetes and metabolic complications among patients with HIV and AIDS

M I Weerakkody¹, K Buddhakorala², N P Somasundaram³


Abstract

HIV infection, as well as its treatment with highly active retroviral therapy (HAART), is associated with a number of metabolic abnormalities such as insulin resistance, glucose intolerance and dyslipidaemia. The aim of this descriptive cross sectional study was to describe the prevalence of diabetes, impaired fasting glucose, dyslipidaemia and obesity among patients with HIV or AIDS who were followed up at the National Sexually Transmitted Diseases (STD) campaign in the year 2010, and to assess the associated factors.

A total of 268 patients were evaluated of which 57.8% were male. Fifty six percent were on HAART therapy. Eighteen patients (6.7%) were diabetics and forty nine (18.3%) had impaired fasting glucose. Only about 40% of the diabetic patients were followed up regularly. About 20% of the patients had high total cholesterol levels (>240mg/dl) and only 24.4% patients had an optimal LDL cholesterol level of <100 mg/dl. 15.3% of the patients had high serum triglyceride levels (200-499mg/dl) and 1.9% had very high triglyceride levels (>500 mg/dl). Fourteen percent of the patients were obese according to the WHO criteria for body mass index for Asians. Being on HAART therapy was significantly associated with having high total cholesterol levels, high LDL cholesterol levels and high triglyceride cholesterol levels but not with elevated blood glucose values in the X² test (p<0.05). The mean total cholesterol, LDL cholesterol and triglyceride levels were also significantly different among HAART users and non users. Having HIV for more than 3.1 years (more than the median) and duration of HAART therapy for more than 1.9 years (more than the median) were also significantly associated with high total cholesterol and LDL cholesterol levels (p<0.05).

Metabolic abnormalities are common among HIV infected persons and some of them are associated with the duration of HIV and the use of HAART therapy.

Introduction

The introduction of the highly active antiretroviral therapy (HAART) has changed the course of HIV infection, increasing survival and improving quality of life in HIV-infected individuals. The search for new therapeutic modalities and management strategies has reduced the acute morbidity of the disease but has created a number of chronic effects. A number of metabolic abnormalities are associated with HIV management; the most common being insulin resistance, glucose intolerance, dyslipidaemia, changes in body fat distribution and osteopenia.

Insulin resistance rather than insulin deficiency is responsible for pathogenesis of diabetes in HIV infected persons. Increased levels of intrahepatic tumour necrosis factor and hepatic steatosis leads to insulin resistance and diabetes, even in patients not on HAART therapy (1). The major contributor to hyperglycemia in HIV/AIDS however, is drugs. Highly active retroviral therapy (HAART) has contributed immensely to the remarkable clinical outcome of HIV patients, but it has also lead to an increase in metabolic dysfunction, insulin resistance, diabetes dyslipidaemia and lipodystrophy (2). A recent analysis found that diabetes is four fold more common in HIV infected men exposed to highly active anti retroviral therapy (HAART) than in HIV seronegative men (3). Diabetes may also be caused by drugs used to manage co morbidities associated with HIV such as Pentamidine used for Pneumocystis Jeroveci infection and Megesterol acetate used as an appetite stimulant (4, 5).

During the course of HIV infection and acquired immunodeficiency syndrome (AIDS), disturbances of lipid metabolism were observed long before the introduction of Protease Inhibitor (PI) based antiretroviral regimens, and included hypertriglyceridaemia and a decrease in total and high-density lipoprotein (HDL) cholesterol, occurring in advanced phases of HIV infection (6). Even though therapy with zidovudine, lamivudine, stavudine, or non-
nucleoside-reverse transcriptase inhibitors (NNRTIs) has been associated with the occurrence of dyslipidaemia, abnormalities of plasma lipid levels appear to be most prevalent among patients receiving a PI-based regimen and ranges from 28% to 80% (6). Among non-PI drugs, Efavirenz and Stavudine lead to Triglyceride elevation, whereas Tenofovir may reduce the Triglyceride level. LDL-C levels are increased in association with most PI- and NNRTI-based regimens (7).

Treatment of these cardiovascular risk factors is of paramount importance in the management of HIV, because studies show that the relative rate of MI hospitalization in HIV-infected persons was more than 2-fold greater than that of controls (7). Management of metabolic complications poses a number of challenges in coexistent HIV infection. Poly pharmacy, co-existing renal and hepatic disease, induction of cytochrome induction pathways with certain antiretroviral drugs causing toxicity of drugs such as statins, the necessity for strict adherence to universal precautions with insulin therapy and the reluctance of caregivers for invasive procedures like administering insulin are some of them. These patients would also be reluctant to seek medical advice or comply for long-term follow-up for these metabolic problems due to the social stigma that is still associated with HIV infection in this part of the world.

Sri Lanka has about 1600 reported HIV infected persons at present with an estimated 4200 of both reported and unreported cases (8). They are followed up in several clinics around the country, the clinic at the National Sexually Transmitted Diseases (STD) Campaign has the largest population of patients, it has followed up a total of 820 patients since its inception in 1997. A total of 369 patients had attended services in the clinic in 2010. Prevalence of diabetes and metabolic abnormalities among patients with HIV/AIDS in Sri Lanka has not been assessed previously.

The aim of this study was to describe the prevalence of diabetes, impaired fasting glucose and other metabolic complications such as dyslipidaemia and obesity among the HIV-infected patients being followed up at the National STD Campaign. It was also aimed at assessing any factors associated with the above metabolic parameters and assessing any correlation between antiretroviral therapy and metabolic parameters.

Method

This was a descriptive cross-sectional study carried out at the National STD Campaign clinic in Colombo. The HIV patients who had attended services at the above clinic during the calendar year 2010 were recruited to the study. This included newly diagnosed patients as well as patients who were diagnosed prior to that but had attended the clinic during 2010. All HIV-infected patients aged 18 and older were included in the sample regardless of being on HAART or not but patients who had not had at least two clinic visits in 2010 were excluded. Ethical approval was obtained from the Ethical Review Committee, Faculty of Medicine, University of Colombo.

As the patients in the clinic routinely undergo biochemical screening at least 3 to 6 monthly, the data on fasting blood glucose and serum lipids were obtained from these records. The anthropometric data (height, weight), which are routinely recorded by the trained nursing officer at the clinic was also obtained from patient records. Data on HAART was taken from medical records and patients were considered to be HAART positive if they were on drugs for at least two months.

Diabetes and impaired fasting glucose were defined according to the ADA 2012 criteria (9), lipids were categorized according to NCEP-ATP3 (10) criteria, and obesity was described according to the WHO classification of obesity for Asians (11). Descriptive statistics were used according to the distribution of the variable: for variables with a normal distribution, occurrence measures, mean and standard deviation values were shown; for non-parametric variables, quartile ranges and median values were shown. Independent sample t test was used to compare means and the associations between metabolic parameters and patient and disease related factors were assessed using the Pearson’s chi-square test. Multivariate linear regression analysis was used to assess the contribution of the different patient, disease and treatment related factors to the metabolic parameters. The P value was considered to be significant at <0.05.

Results

This study included 268 patients with HIV or AIDS, 57.8% were males (n = 155). The median age was 41 years and the ages ranged from 20 to 73 years. One hundred and fifty one patients were on antiretroviral therapy (56.3%) and the commonest combination of drugs was Zidovudine, Lamivudine and Efavirenz (2 nucleoside reverse transcriptase inhibitors and 1 non nucleoside reverse transcriptase inhibitors), 52% of the patients had been on this combination for more than 2 months. Only 7.2% were on protease inhibitor based HAART regimes.

This population had 18 diabetic patients (6.7%) and 08 (3%) of them were known diabetics at the diagnosis of HIV. Forty nine patients (18.3%) had impaired fasting glucose by the ADA definition. Only 7 (38.9%) of the diabetic patients were on regular follow-up regarding diabetes; however 78% were taking either oral hypoglycaemic drugs or insulin. Only 6 (33.3%) had target organ screening done and half of those patients had evidence of microvascular disease.
Table 1. Basic, disease and treatment characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no of patients</td>
<td>268</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>155 (57.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>113 (42.2%)</td>
</tr>
<tr>
<td>Median age in years (25-75 range)</td>
<td>41 (33-46)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>54 (20.1%)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>10 (3.7%)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>204 (76.1%)</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>12 (4.5%)</td>
</tr>
<tr>
<td>Mean CD4 count at HIV diagnosis</td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>390 (242.7)</td>
</tr>
<tr>
<td>200-500</td>
<td>59 (24.8%)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>104 (43.7%)</td>
</tr>
<tr>
<td>Median Duration of HIV in years (25-75 range)</td>
<td>3.12 (1.5-5.58)</td>
</tr>
<tr>
<td>Median Duration of clinic follow-up years (25-75 range)</td>
<td>2.67 (1.1-5.22)</td>
</tr>
<tr>
<td>On anti retroviral therapy</td>
<td>151 (56.3%)</td>
</tr>
<tr>
<td>Median Duration of anti retroviral therapy – years (25-75 range)</td>
<td>1.91 (0.83-4.67)</td>
</tr>
<tr>
<td>Type of anti retroviral therapy</td>
<td></td>
</tr>
<tr>
<td>Nucleoside reverse transcript inhibitors</td>
<td>145 (96%)</td>
</tr>
<tr>
<td>Non nucleoside reverse transcript inhibitors</td>
<td>143 (94.7%)</td>
</tr>
<tr>
<td>Nucleotide reverse transcript inhibitors</td>
<td>22 (14.6%)</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>11 (7.2%)</td>
</tr>
<tr>
<td>Diabetics</td>
<td>18 (6.7%)</td>
</tr>
<tr>
<td>Known diabetics at HIV diagnosis</td>
<td>08 (3.0%)</td>
</tr>
<tr>
<td>Diabetes diagnosed during follow up</td>
<td>10 (3.7%)</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>18 (3%)</td>
</tr>
<tr>
<td>On Statin therapy for &gt; 3 months</td>
<td>19 (07%)</td>
</tr>
</tbody>
</table>

The metabolic characteristics of the population studied is described in Table 3.

Forty nine (23.6%) of the non diabetic population had impaired fasting glucose and 78% of the diabetic patients (no=14) had fasting blood glucose above 110 mg/dl despite being on treatment.

About 20% of the patients had high total cholesterol levels (>240mg/dl) and only 24.4% patients had an optimal LDL cholesterol level of <100 mg/dl. 15.3% of the patients had high serum triglyceride levels (200-499mg/dl) and 1.9% had very high triglyceride levels above 500 mg/dl. Only 12.2% (no=27) of the patients had low HDL cholesterol levels of less than 40mg/dl.

One hundred and eight patients (44.6%) had normal body mass index (BMI) according to the WHO classification of body mass index for Asians (11). However 14% of the patients were overweight and 18.2% of the patients were obese according to the same criteria.
The associations between various metabolic parameters and patient and disease characteristics such as age, gender, smoking habits, body mass index, lowest CD4 count at diagnosis, duration of HIV, whether on HAART therapy and duration of HAART therapy was also assessed.

Being on HAART therapy was significantly associated with having high total Cholesterol levels, high LDL cholesterol levels and high triglyceride cholesterol levels in the X² test (p<0.05). The mean total cholesterol, LDL cholesterol and triglyceride levels were also significantly different among HAART users and non-users (Table 3). Having HIV for more than 3.1 years (more than the median) and duration of HAART therapy for more than 1.9 years (more than the median) were also significantly associated with high total cholesterol and LDL cholesterol levels (p<0.05). However, when the multiple regression model was used, none of the above characteristics were associated with high total cholesterol, LDL cholesterol or triglyceride levels.

Figure 1. Metabolic characteristics of patients.
Table 2. Metabolic parameters among HAART users and non-users

<table>
<thead>
<tr>
<th></th>
<th>On HAART therapy</th>
<th>Not on HAART therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>97.47(29.53)</td>
<td>90.88(21.11)</td>
<td>0.24</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>212.94(44.98)</td>
<td>187.64(33)</td>
<td>0.006</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>172.56(131.25)</td>
<td>118.24(52.21)</td>
<td>0.000</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>128.86(38.32)</td>
<td>117.65(28.46)</td>
<td>0.008</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>51.09(10.2)</td>
<td>46.25(8.75)</td>
<td>0.831</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.72(3.96)</td>
<td>21.09(3.84)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Statistics: independent sample t test, p <0.05 significant

Discussion

This descriptive study, the first to be done on HIV patients in Sri Lanka, describes a prevalence of 6.7% for diabetes and 18.3% for impaired fasting glucose in this population. There was a baseline prevalence of diabetes in 3% of this study population. In the Sri Lanka Diabetes Cardiovascular Study, a population based study involving 7 provinces of Sri Lanka, the prevalence of diabetes and impaired fasting blood glucose were 10.3% and 4.4% respectively (12). Our population had lower prevalence of diabetes but the prevalence of impaired fasting glucose was about 3 times higher (12). However the mean age of that population was 46.1 (standard deviation 15), while our population had a lower mean age of 40.3 years (standard deviation 9.3). Previous studies assessing the prevalence and the incidence of diabetes and impaired glucose tolerance have shown a wide range of values. DAD study, one of the largest, multicentre cohort studies designed to assess the association between HAART therapy and cardiovascular disease, had a baseline prevalence of diabetes in 2.85% of the population. The new onset diabetes was 2.2% (5.72 at 1000 person year follow up) (13). Other smaller studies with heterogeneous study designs, which included patients with and without HAART therapy, reported a prevalence of diabetes ranging from 4.5% to 7%, and impaired fasting glucose ranging from 17% to 35% (14, 15, 16). Although most studies show that the prevalence of diabetes and impaired glucose tolerance is higher in HIV infected patients than in the normal population, a few studies have shown that there is no difference (17). In Nutrition for Healthy Living Study, a large multicentre cohort study in the US, a non diabetic subgroup was analyzed to assess the prevalence of insulin resistance by using a number of insulin resistance indices and serum insulin levels and was compared with the national NHANES111 database. The prevalence of insulin resistance varied from 17%-51% depending on the indices used, but it was not different to the control population in the NHANES111 (17). The wide variation of glucose parameters in different studies could be due to the different study designs, inclusion of both HAART positive and negative populations, different types of HAART drugs used (sp Protease Inhibitors), the characteristics of the control group and patient characteristics such as the presence of lipodystrophy. Some studies have used basic biochemical parameters such as fasting blood glucose and the oral glucose tolerance test whereas other studies have used measures of insulin resistance such as the HOMA index and QUICKI score. While some control groups consisted of healthier people such as blood donors other controls have been taken from national databases.

Studies have also demonstrated that the prevalence of diabetes and impaired fasting glucose is higher among HAART users when compared to HAART non users (3, 13, 18). The most commonly studied drug to be associated with HAART therapy is Protease Inhibitors. Several large scale studies among HIV patients describe a prevalence of impaired glucose tolerance ranging from 8-46% among Protease Inhibitor users (19) out of which Ritonovir is found to be the most commonly associated agent (3, 13). Others studies have demonstrated that the use of Nucleoside Reverse Transcriptase Inhibitors (especially Stavudine) is associated with a higher incidence of glucose abnormalities (20, 21). Other factors that were associated with diabetes mellitus and impaired glucose tolerance were patient characteristics such as age, gender, body mass index and family history of diabetes mellitus and disease related factors such co infection with hepatitis C, duration exposure to HAART therapy and CD4 count of < 300 cells/μl at the index visit (3,13, 20). In our study there was no statistical difference in the mean fasting blood glucose levels among the HAART users and non users. Factors such as the CD4 count at diagnosis, the duration of HIV infection, and the duration of antiretroviral therapy were
also not associated with elevated blood glucose levels either. One explanation for not finding an association between HAART use and elevated blood glucose levels in our study could be that only 7.2% of our patients were on Protease Inhibitors and only 11% were on Stavudine, the most commonly cited drugs to be associated with blood glucose abnormalities. However even in our patient population, 35.5% of the Stavudine treated patients had impaired glucose tolerance (vs. 18% of the study population) and 27.3% of the Protease Inhibitor group had fasting blood glucose >126 mg/dl (vs. 4.1% of the study population).

It is important to note that only 38% of the diabetic patients had regular follow-up regarding diabetes and 22.2% were not taking any form of therapy for the illness. Target organ screening was done only on 6 (33.3%) of the diabetic population. Factors such as experience of drug interactions, polypharmacy, social stigma and unawareness regarding the long-term complications of diabetes may be responsible for the poor compliance to therapy. These issues need further evaluation and planning out of possible solutions.

The classic dyslipidaemia associated with HIV infection, with high total cholesterol, LDL and triglyceride levels and low HDL cholesterol is also shows different prevalence in different studies. In a French study of 925 patients, 70 patients (8%) experienced high triglyceride levels after 25 months of follow up, and a prospective population study from Canada quotes a cumulative incidence of dyslipidaemia of 9% within 31 months of commencing HAART therapy (19). Studies in other parts of the world show higher prevalence and incidence of dyslipidaemia. In a comparison study in Brazil 41.4% and 20.5% of the patients on HAART showed high triglyceride and total cholesterol levels respectively. Compared to HIV patients not on HAART this was statistically significant (22). The same study shows that all HAART regimens can alter the lipid parameters although Ritonovir based therapy had the highest risk (22). Another study in Thai patients showed that patients on Protease inhibitors had higher Total cholesterol, Triglyceride and low HDL levels (42.6%, 75.4%, 31.2% respectively) when compared to patient not on treatment (4.8%, 8.2%, 42.95% respectively). Patients on other HAART drugs had in-between values of 26.6%, 48.3% and 20% respectively (23). Although less well studied, other HAART drugs such as nucleoside reverse transcriptase inhibitors (NRTIs), Nonnucleoside reverse transcriptase inhibitors (NNRTIs), mainly Efavirenz might also be associated with metabolic disorders, including dyslipidaemia (24). In our study 15.3% of the patients had high (>240 mg/dl) total cholesterol, 13.4% high triglyceride (>200 mg/dl) and only 10.1% had low HDL cholesterol (40 mg/dl). The somewhat lower values in our study population may be due to the low use of protease inhibitors in our patients (7.2%). However among our patients who were on Protease Inhibitors, 63% had total cholesterol >240 mg/dl and 45% had triglycerides >200 mg/dl compared to 22% and 14.2% of patients who were on other HAART drugs. The onset of dyslipidaemia is said to be between 3 to 12 months in Protease Inhibitor based regimes (6) but the onset of dyslipidaemia with other drugs is not well documented. Therefore, as the median duration of HAART treatment (with mainly non Protease Inhibitor based therapy) is only 1.9 years in our study, that may be one reason to get lower lipid values than in certain studies. Most other studies in literature assessing the prevalence of hyperlipidaemia has either excluded the patients on lipid lowering therapy or has not mentioned whether they have done so. 7% of our patients were on treatment for hyperlipidaemia, which may have contributed to the lower values of lipid abnormalities in our study compared to some other Asian and South American studies. However, the mean total cholesterol, triglyceride and LDL levels were significantly higher in patients with HAART therapy in our study, when compared to patients not on HAART therapy. The duration of HIV infection for more than 3.1 years and being on HAART therapy for more than 1.9 years were significantly associated with having abnormal lipid levels as well.

In this patient population, 14% were overweight and 18.2% were obese according to the WHO classification of obesity for Asians. Overweight and obese patients in patients younger than 40 years were 10.3%, 14.3% and in patients 40 years of age or older were 14.8%, and 18.3% respectively. A descriptive study in 7 provinces of Sri Lanka revealed that 25.2% of people were in overweight and 9.2% were in the obese categories using the WHO criteria for Asians (25), which are higher figures than in our study. Age and gender related figures were also higher in that study. In the D.A.D sub study assessing metabolic syndrome as a cardiovascular risk factor, only 4.4% of the sample had BMI >30 kg/m² (26). Studies elsewhere in the world have shown prevalence of obesity ranging from 4% to 35% (27, 28). Studies have also shown that waist circumferences were lower in HIV-infected HAART recipients compared with the uninfected population despite having similar prevalence rates for metabolic syndrome. In one study, although 50% of HIV-infected HAART recipients met non-anthropometric criteria for metabolic syndrome, this reduced to 17% when waist-based anthropometric cutoffs were applied (29). Therefore HIV infected patients, although having other metabolic risk factors may not be an obese population. The possible explanations for these findings could be the presence of co-existing chronic infections such as tuberculosis, malabsorption syndromes associated with the disease as well as HAART, and although much rarer now, the HIV wasting syndrome resulting in lower body mass indices. The differences in overweight and obesity prevalence among studies may also be influenced by the differences in ethnicity, gender, socio-economic status and the nutritional status of the population.
There are several limitations in this study. Data were mainly extracted from records due to reasons in confidentiality resulting in a significant amount of incomplete and missing data and inaccuracies in anthropometric values. Ours was a cross sectional study; a prospective study would have been the best study design to assess the effect of HIV and HAART therapy on metabolic parameters. HIV associated lipodystrophy syndrome, known to be present sometimes in up to 80% of the patients on HAART therapy (16, 19), and having higher correlation with insulin resistance and metabolic abnormalities was not assessed in our study. Its presence or absence would have had a greater influence on some of our metabolic parameters.

In conclusion this study highlights the high prevalence of impaired fasting glucose in patients followed up at the National STD and AIDS campaign and the strong association of HAART therapy with dyslipidaemia in the same group. It also emphasizes the necessity of proper treatment and follow-up of HIV positive patients with diabetes. This data would probably help in planning out management strategies for the above group of patients and also would help in carrying out similar studies on HIV patients on a national level.

References


Clinical update

Evaluation and management of precocious puberty

Navoda Atapattu¹, K S H de Silva²


Abstract

Puberty is an important event in adolescence. Altered timing of puberty brings about anxiety and fears in both the child and parents. Precocious puberty is usually idiopathic in a girl whereas a secondary cause needs to be excluded in a boy. Diagnosis and management require a careful evaluation in a logical sequence. The normal variants of puberty may not need extensive investigations but child will have to be followed up. The diagnostic and therapeutic approaches to a child with precocious puberty are discussed in this article.

Introduction

Puberty is the process of physical, hormonal and psychological changes in a child’s body facilitating the reproductive capabilities. Pubertal changes are triggered by sex hormones following activation of the hypothalamo pituitary gonadal axis.

Genetic and environmental factors are implicated in the timing of puberty (1). Human studies have shown a relationship between body mass index or body fat, dietary and physical activity with the timing of puberty (2, 3, 4). More recently a G-protein coupled receptor, GPR54 and its ligand Kisspeptin have been identified as important signals in pubertal induction (5). The role of leptin in the pubertal induction is permissive rather than definitive and there are many unanswered questions in relation to role of leptin (6).

Precocious puberty

Precocious puberty has been traditionally defined as development of secondary sexual characteristics before 9 years in a boy and before 8 years or menstruation before 9.5 years in a girl. However there has been a secular trend towards early pubertal development (7).

Based on 1997 Pediatric Research in Office Settings (PROS) network study Kaplowitz and Oberfield (8) recommended to reset the age limit for precocious puberty to breast development at 7 years in Caucasian girls and 6 in African-Americans. However, due to the dissociation of age of breast development and age at menarche, this opinion was not accepted by many. A recent review by Midyett et al (9) reported 12 % of black girls to have non idiopathic sexual precocity between 6 and 8 years.

There are two types of precocious puberty.

1. Gonadotrophin dependent precocious puberty (CPP) or central/true precocious puberty.

   This is when pubertal signs are consonant but may be more rapid in progression than in normal puberty.

2. Gonadotrophin independent precocious puberty or sexual precocity.

   This is diagnosed when there is no activation of the hypothalamo pituitary gonadal axis and signs of puberty are not consonant.

Diagnosis

A detailed history is a prerequisite in the diagnosis and management of a child with precocious puberty. If more than one pubertal signs are present and growth is accelerated with advanced bone age, investigations are needed to confirm the diagnosis. In isolated vaginal bleeding the possibility of sexual abuse, foreign body or nonspecific vaginitis should be considered. Exposure to exogenous oestrogen in the form of creams, pills should also be excluded.

Pubertal staging, anthropometry, presence of café au lait patches and examination of the systems including testes are important aspects in the examination.

The height should be compared with the mid parental height and heights of siblings.

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The following investigations are indicated to confirm the clinical diagnosis of precocious puberty:

1. **Bone age**
   Bone age is advanced in precocious puberty but may be delayed in gonadotrophin independent precocious puberty due to untreated hypothyroidism (Van Wyk-Grumbach syndrome) (10).
   On average, bone age is 10.75 years at the onset of puberty and 13 years at menarche. Testicular volume of 4 ml is seen at the bone age of 11.5 years (11).

2. **Sex hormone levels**
   Testosterone >25ng/dl or oestradiol >10pg/ml are suggestive of precocious puberty.
   If the oestradiol levels are in the upper end of normal range (75pg/ml), it is necessary to exclude an ovarian or adrenal tumour (12).

3. **Gonadotrophin releasing hormone (GnRH) stimulation test.**
   The response after 20 and 60 minutes of intravenous 100ug of GnRH can be used to differentiate the two types of precocious puberty. Luteinising hormone (LH) predominant response will be seen in gonadotrophin dependent precocious puberty (CPP). There will be no response or a FSH predominant response in gonadotropin independent precocious puberty.
   In the absence of this investigation a FSH/LH assay done at midnight will show the sleep associated rise in LH in CPP.
   The following published data are useful in the interpretation of the gonadotrophin levels using the chemiluminescent assay:
   - In gonadotrophin dependent precocious puberty; LH/FSH >1 (13)
   - Peak LH response > 5U/L from baseline (14)
   - FSH has a poor diagnostic utility (15)
   - Basal LH >0.1 IU/L was diagnostic for CPP with 94% sensitivity and 88% specificity (16).

4. **Ultrasound scan of the abdomen (USS)**
   This is a useful investigation to differentiate CPP from gonadotrophin independent puberty.
   - In CPP uterine length ranges from 3.4-4cm and the range of ovarian volume is between 1-3ml in (18).
   - Endometrial echo is 100% specific but less sensitive (42-87%) in differentiating CPP (18).
   - Adrenal hypertrophy will be seen in precocious puberty due to CAH.
   - Multicystic ovaries will be seen in hypothyroidism.

5. **When clinically indicated adrenal androgens or thyroid function tests are useful to identify the cause of gonadotrophin independent precocious puberty.**

6. **Magnetic resonance image (MRI)**
   Hypothalamic hamartoma is the commonest central nervous system pathology associated with CPP.
   All boys with CPP and girls < 6 years should have an MRI of the brain. It is questionable whether it is useful in girls between 6-8 years.
   It is useful to know that the size of the pituitary is large for the chronological age in CPP; correlates with LH/FSH ratio as this knowledge will avoid misdiagnosis of pituitary adenoma (19).

7. **Insulin like growth factor (IGF1)**
   This is not a routine investigation. But it has been found to be raised in CPP (20).

**Management**

Treatment with a gonadotrophin releasing hormone (GnRH) analogue is only effective in gonadotrophin dependent precocious puberty. Initially the progression of puberty can wax and wane. Therefore in the absence of an identifiable central nervous system pathology and a rapid progression of symptoms and signs, treatment can be withheld with close monitoring of the patient.

Local sterile abscess, hot flushes with headache, weight gain and mild hypersensitivity reactions are the reported side effects which occur rarely.

Pubertal staging and growth velocity need monitoring every 3-6 months. Reduction of breast or testicular size may be noted on follow up.

The decision to stop treatment is based on the age of puberty of peers, siblings and parents and wishes of the patient and family. Discontinuation of treatment at chronological age 11 years (bone age 12) has been associated with maximal adult height (21). It is not recommended to continue treatment beyond 12-12.5 years of chronological age.

Once treatment is stopped menstruation will commence 2-61 months later (22).

The decision to commence treatment therefore would depend on the rapidity of the progression of puberty, the presence of CNS pathology and the age of the child. The short and long term implications of treatment should be discussed with the parents prior to treatment.

The treatment is with a long acting GnRH analogue.
There are several subcutaneous and intramuscular preparations and in addition an intranasal preparation.
Clinical update

In a girl the treatment is combined with norethisterone for initial 1-2 weeks to prevent withdrawal bleeding.

A height loss of 20 cm in boys and 12 cm in girls has been documented in untreated patients (23). Girls <6 years gain a greater benefit from treatment (24). Girls between 6-8 years may have a modest benefit. It is necessary to discuss with the family in borderline cases before commencing treatment. All boys < 9 years with compromised adult height warrant treatment. Treatment solely for psychological reasons or cessation of menses should be individually assessed.

Long term effects

BMD reduces during therapy but once the treatment is discontinued normal peak bone mass is gained provided they have an adequate calcium and vitamin D intake. GnRH therapy is associated with an increased risk of PCOS (25). Long term studies have revealed that GnRH therapy has no adverse effect on fertility (26).

Psychological support should be offered to the parents and child if needed.

Gonadotrophin independent precocious puberty

McCune-Albright syndrome (MAS)

MAS is defined as a triad of precocious puberty, fibrous dysplasia of bones, and café-au-lait macules caused by an activating mutation of the GNAS1 gene. Precocious puberty is the most common endocrine abnormality though rare in males. GnRH analogues are ineffective as a treatment. Aromatase inhibitor, anastrozole has been used with success and tamoxifen, an antiestrogen has been found to be beneficial in girls. The use of testolactone in combination with spironolactone or flutamide appears to be effective in boys (27). Third generation aromatase inhibitor letrozole has been shown to be effective in treating girls with MAS even though ovarian enlargement or cyst formation may be seen in patients on higher doses (28).

Testotoxicosis (Familial male precocious puberty)

Testotoxicosis occurs due to a heterozygous mutation of the luteinizing hormone receptor gene resulting in constitutive activation of the LH receptor giving rise to autonomous Leydig cell hyper function. Affected boys generally present before 4 years of age. Testolactone and spironolactone have been shown to be effective in the long term treatment (29). Combined therapy with a third generation aromatase inhibitor (anastrozole) and the selective anti-androgen bicalutamide (non-steroidal anti-androgen) was used with promising results in the recent past (30).

Variants of puberty

a. Premature thelarche

Premature breast development before 3 years of age is defined as premature thelarche which may be unilateral or bilateral. Puberty occurs at the normal age and there is no advance in the bone age. The condition spontaneously resolves by 4 years of age.

The larche variant

The Majority of these patients present between 7-8 years of age. They have an advanced bone age and an increase in the height velocity. They do not need treatment and the final adult height is not affected.

b. Premature adrenarche

Premature adrenarche is defined as the presence of secondary sexual hair in girls < 8 years and boys < 9 years. This is more frequently seen in girls and in children from African or Indian origin. CAH and adrenal tumour need exclusion before the diagnosis of premature adrenarche is made. This may be associated with low birth weight, insulin resistance and PCOS. No specific treatment is needed and their final height is normal.

c. Isolated menarche

Isolated menarche is a benign self-limiting condition. They present with recurrent vaginal bleeding without secondary sexual characteristics. A localised lesion of the genital tract, McCune-Albright syndrome, exogenous administration of oestrogens and child abuse need exclusion. There are no long term sequelae associated with this condition.

References


Evaluation and management of precocious puberty


Clinical update

Glucocorticoid-induced osteoporosis; management based on recent major international recommendations

Amila Rathnapala¹, Noel Somasundaram²


Abstract

Osteoporosis is one of the important adverse effects of glucocorticoids causing significant disability due to fractures. Fracture is the presenting feature in 30-50% of patients with Glucocorticoid-Induced Osteoporosis (GIO). A rapid decline in bone mineral density (BMD) occurs in the first six months with the use of glucocorticoids.


All three guideline committees recommend counseling for lifestyle modification, risk assessment and adequate calcium and vitamin D supplementation.

The ACR expert panel has recommended the FRAX tool for the risk stratification. It considered the glucocorticoid dose as an average dose. However, there is strong evidence that the risk associated with glucocorticoid use is dose related. Considering that, IOF proposed a FRAX adjustment for the dose of glucocorticoids.

Even though there is evidence for the bisphosphonate therapy for patients with more than 50 years of age, there is a significant paucity of evidence for age less than 50 years group. ACR only recommends bisphosphonate therapy for the patients below 50 years with fragility fractures. But ASBMR recommends bisphosphonate therapy for patients below 50 years with Z-score less than – 2 or if there is a significant risk of BMD loss. But the IOF has recommended the use of bisphosphonates based on clinical background and adjusted FRAX score.

Introduction

Osteoporosis is one of the important adverse effects of glucocorticoids causing significant disability due to fractures. We discuss the management strategies available to prevent and treat Glucocorticoid-Induced Osteoporosis (GIO) based on the American College of Rheumatology (ACR) Guidelines 2010 (1) and American Society of Bone Mineral Research (ASBMR) recommendations 2011(2) and International Osteoporosis Foundation (IOF) Guidelines 2012(3).

Case vignette

A 43 years old male with a past history of nephrotic syndrome secondary to minimal change disease in 2009, presents with proteinuria of 5g/day and body swelling for one week. He had two similar episodes in the past which was treated with prednisolone 45 mg/day for more than a year. He does not have a family history of fragility fractures.

He smokes 5 cigarettes daily for last 20 years (4 pack years).

His weight when he was not oedematous was 50 kg and the body mass index (BMI) was 19.5 kg/m².

Current episode was diagnosed as the third relapse of nephrotic syndrome and he was commenced on oral prednisolone 50 mg daily with calcium lactate 300mg three times daily. He was also treated with captopril and losartan. His creatinine clearance was 96 ml/min.

How should this patient be evaluated and managed to minimize the risk of fractures?
Glucocorticoid-induced osteoporosis

The clinical problem

Glucocorticoid use is one of the leading risk factors for osteoporosis (4, 5) and fracture. It is known that fracture can be the presenting feature in 30-50% of patients with GIO (6). The loss of bone mineral density (BMD) in patients treated with glucocorticoids is biphasic. A rapid decline occurs in the first year and more slowly thereafter (7, 8). An increased risk of fractures has been reported with dosages of prednisolone (or equivalent) as low as 2.5-7.5 mg daily. This increased risk may relate more strongly to daily rather than cumulative doses of glucocorticoids (9, 10). In a retrospective study involving patients 18 to 64 years of age, continuous treatment with 10 mg of prednisolone per day for more than 90 days, for various indications, as compared with no exposure to glucocorticoids demonstrated a 5-fold increased risk of hip and 5.9-fold increased risk of vertebral fracture. The combined effect of higher dose and longer duration, further increased relative risk to 7-fold for hip and 17-fold for vertebral fractures (11). In addition, an increase in the risk of fractures has been reported with the use of inhaled glucocorticoids, as well as with alternate-day and intermittent oral regimens (5).

Risk assessment

Risk assessment is the most important step in the prevention and management of GIO.

The history should specifically focus to assess level of smoking, alcohol consumption, frequency of falls and family history of osteoporosis. The BMI calculation and neurological examination are essential components. It is always important to document the baseline height as asymptomatic vertebral fractures can be suspected with height monitoring.

It is also important to screen for secondary causes for osteoporosis such as renal impairment, chronic liver disease, hyperthyroidism and hypogonadism in clinically relevant cases.

The ACR expert panel has recommended the FRAX tool for the risk stratification (1). This tool uses updated, evidence-based estimates of absolute 10 year fracture risk (1). It was created for the purpose of integrating numerous risk factors into a clinically useful risk prediction model (12).

The FRAX tool considered the steroid dose as an average dose. However, there is good evidence that the risk associated with glucocorticoid use is dose related. It uses only the bone density value for the hip, but patients receiving glucocorticoids frequently lose bone mass in the spine before the hip, leading to a possible underestimation of fracture risk. Because of this some authors do not recommend FRAX as a tool for risk assessment in GIO (13). But IOF expert committee has proposed a FRAX adjustment for the dose of steroids. The evidence came from the General Practice Research Database (GPRD) in UK, which has demonstrated that fracture risk is increased even with relatively low daily doses of glucocorticoids and rises further with increasing daily dose (14). The detailed FRAX adjustments are shown in Table 1.

Table 1. The average FRAX adjustments for postmenopausal women and men aged ≥ 50 years depending on the steroid dose

<table>
<thead>
<tr>
<th>The steroid dose</th>
<th>FRAX adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5 mg/day prednisolone or its equivalent for hip fracture</td>
<td>0.65</td>
</tr>
<tr>
<td>≥7.5 mg/day prednisolone or its equivalent for hip fracture</td>
<td>1.20</td>
</tr>
<tr>
<td>&lt;2.5 mg/day prednisolone or its equivalent for major osteoporotic fracture</td>
<td>0.8</td>
</tr>
<tr>
<td>≥7.5 mg/day prednisolone or its equivalent for major osteoporotic fracture</td>
<td>1.15</td>
</tr>
</tbody>
</table>

Strategies for prevention of GIO

Smoking cessation, avoidance of alcohol intake, regular physical exercises, calcium and vitamin D supplementation are basic strategies to prevent GIO, although the evidence for their effects on fracture risk is weak. The recommended calcium intake (supplement plus oral intake) is 1200-1500 mg/day and the recommended dose of vitamin D is 800-1000 units per day. A higher dose is recommended as glucocorticoids interfere with vitamin D absorption (15).

In addition to the above, all the guidelines recommend the use of smallest dose of glucocorticoid for the shortest duration possible as there may be no dose of steroids that does not accelerate bone loss or increase fracture risk (16). Alternative strategies should be considered to minimize the steroid dose. Different routes (eg. topical, inhalational) of administration or different formulations may be considered in some occasions. Use of alternative immunosuppressive treatment (eg. azathioprin) may enable reduction of the dose of glucocorticoids.

Monitoring patients receiving steroids

Assessment of compliance to osteoporosis medication, assessment of incidence of fragility fractures and annual height measurement are essential components of monitoring. In some, serial BMD testing can be done.
Pharmacotherapy for the management and prevention of GIO

The IOF committee has recommended their preventive strategies based on clinical and adjusted FRAX score. Even though there is evidence for the recommendations for patients above 50 years of age, there is a significant paucity of evidence for the age group below 50 years (3).

IOF has proposed several principles of GIO management (3). Firstly the bone protection therapy should be started at the onset of steroid therapy and should be withdrawn when the steroid therapy is terminated. Calcium and vitamin D supplementation with adequate dietary intake should be maintained. Alendronate, etidronate, risedronate, zoledronic acid and teriparatide can be used as the front-line therapeutic options for the majority of patients.

In patients who are 50 years and younger, the recommendations are varied across the three guidelines, since data on pharmacological interventions are sparse. But evidence suggests that the fracture risks among young are less compared to the older people. ACR only recommends therapy for the patients who have fragility fractures, however the American Society for the Bone Mineral Research (ASBMR) recommends GIO therapy for patients less than 50 years of age with Z score less than -2 or if there is a significant risk of BMD loss (2). IOF recommends bone protective therapy for young people with previous fragility fractures or who are on high dose of glucocorticoids (3).

Conclusion and recommendations

This patient has several risk factors for GIO, which include current smoking, past history of steroid use and current high dose prednisolone treatment. It is essential to advise and support him quit smoking and to counsel him to have adequate calcium and vitamin D intake with normal protein diet.

At the time of admission, he should undergo DXA (Dual Energy X ray Absorptiometry) scan to assess the BMD.

He should be treated with oral calcium salts 1200-1500 mg daily and oral vitamin D 800-1000 IU per day. There are very few data on the use of glucocorticoids in men at this age group. But considering the disease which requires high doses of steroids for longer duration, he should be treated with bisphosphonates, according to the IOF recommendations.

Alendronate is the first line therapy in Sri Lankan set up, since it is freely available in the public health sector. The dose should be either 70 mg weekly or 10 mg daily. Half dose of alendronate or any other bisphosphonate is not recommended to prevent bone loss in GIO.

The duration of the therapy should be decided carefully because most of the studies done with bisphosphonates have been done for short periods and new potential adverse effects of long-term therapy such as osteonecrosis of the jaw and atypical subtrochanteric fractures have been recognized (17, 18). As studies for the prevention and treatment of GIO lasted no more than 3 years, it is the opinion of the ASBMR Professional Practice Committee that patients requiring longer-term steroid therapy be evaluated for substitution of bisphosphonate treatment with teriparatide, or be considered for treatment with teriparatide initially, followed by treatment with a bisphosphonate (2). But IOF has shown that the benefit of continuation of bisphosphonates is far more than the risk (3). Even though some experts recommend drug holidays when using for longer durations, the current data concerning the appropriateness of it is inadequate due to the small number of studies.

Limitations of the recommended GIO therapy

ACR and ASBMR expert panels are not clear about the individual doses of bisphosphonates. GIO therapies for patients with chronic renal insufficiency are also not adequately discussed. The systemic review of most of the guidelines were only restricted to the European countries and America.

Acknowledgment

We would like to thank Professor Sarath Lekamwasam for his kind advice and assistance.

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Clinical update

Update on subclinical thyroid disease

I Kavinga Gunawardane1, Noel Somasundaram2


Abstract

Subclinical thyroid disease is commonly encountered now as more patients with vague, non-specific symptoms are being evaluated with ultra-sensitive, third generation TSH assays. The clinical significance of mild thyroid over-activity and under-activity is uncertain, which has led to controversy over the appropriateness of diagnostic testing and possible treatment. In this article, we discuss the definition, differential diagnoses, risks of progression, potential health outcomes and management of subclinical thyroid dysfunction.

Introduction

Subclinical thyroid disease is defined as a biochemical disorder with abnormal serum thyrotropin (TSH) and normal serum free thyroxine (T4). These changes of TSH are thought to be due to mild thyroid dysfunction.

Subclinical hypothyroidism

It is defined biochemically as normal free T4 in the presence of an elevated TSH. In population-based studies, the prevalence of subclinical hypothyroidism ranges from 4 to 15%, being higher in females. It’s prevalence rises with age (1).

Subclinical hypothyroidism is more prevalent in areas of iodine sufficiency. A high prevalence of goiter and autoimmune thyroiditis has been observed in Sri Lanka following the salt iodization program, which makes subclinical hypothyroidism a more commonly encountered problem for the clinicians (2).

The causes of subclinical hypothyroidism are the same as those of overt hypothyroidism. Most patients have chronic autoimmune (Hashimoto’s) thyroiditis with high serum concentrations of antithyroid peroxidase (AntiTPO) antibodies (3).

Diagnosis

The diagnosis of subclinical hypothyroidism is based upon biochemical testing alone, with high TSH and normal free T4. Most patients have serum TSH levels <10 mU/L and are asymptomatic.

If the serum TSH concentration is elevated on initial evaluation, it should be repeated along with a free T4 after 3 to 6 months to confirm the diagnosis. However, in circumstances where there is a strong indication for thyroxine therapy, such as, the presence of a goiter, positive anti TPO antibodies, pregnancy, infertility or planning a pregnancy, diagnosis and treatment can be initiated earlier.

Differential diagnosis

There are several causes of a high serum TSH concentration that do not properly fit the definition of subclinical hypothyroidism. One such instance is during the period of recovery from nonthyroidal illness, where a transiently elevated serum TSH can be detected. Also following the hyperthyroid phase of thyroiditis, a transient, mild hypothyroidism is usually seen. Assay variability and rarely, the presence of heterophilic antibodies must also be considered. Untreated adrenal insufficiency is another important diagnosis to exclude. In central hypothyroidism up to 25% of patients have a mildly elevated TSH and a low or low-normal free T4 and rarely, thyroid hormone resistance can give a similar biochemical picture.

Evaluation

Some patients with subclinical hypothyroidism have mild non-specific symptoms such as fatigue and constipation. Thus, patients with subclinical hypothyroidism should be questioned about symptoms of hypothyroidism, past treatment for hyperthyroidism and use of medications that may impair thyroid hormone absorption or function. Drugs such as lithium, amiodarone,

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interferone alfa and radiographic agents can interfere with thyroid functions. Antithyroid peroxidase antibodies are not routinely measured in patients with subclinical hypothyroidism, however, the presence of antibodies may be useful when deciding either to treat or to monitor.

**Management**

Although virtually all experts recommend treatment of patients with serum TSH concentrations >10 mU/L, the routine treatment of asymptomatic patients with TSH values between 4.5 and 10 mU/L remains controversial. The clinical guidelines by the Endocrine Society of Sri Lanka recommends to repeat TSH in 3 to 6 months in patients with TSH between 4.5-10 mU/L prior to commencement of thyroxine (4). In view of data linking subclinical hypothyroidism with atherosclerosis and myocardial infarction, young or middle aged patients with TSH between 4.5 and 10 mU/L can be treated in the presence of symptoms, a goiter, high titers of antithyroid peroxidase antibodies and dyslipidaemia.

One should be cautious about over-treatment with T4 which may result in adverse consequences, such as cardiac arrhythmia, especially in the elderly.

Synthetic thyroxine is the treatment of choice for correction of hypothyroidism. For elderly patients and those with underlying cardiovascular disease, the initial dose of thyroxine is typically 25 to 50 mcg/day. This approach will avoid over-treatment. Younger patients, without a history of thyroid autonomy, can be initiated at a dose slightly below full replacement (1.6 mcg/kg/d).

Initiating thyroxine replacement should be done early in women with TSH values >4.5 mU/L who are either pregnant, wish to become pregnant or have ovulatory dysfunction and infertility.

The goal of therapy is to reduce the patient’s serum TSH to the normal reference range. Many experts recommend a therapeutic TSH target of 0.5-2.5 mU/L in young and middle-aged patients while a TSH target of 3 to 5 mU/L may be appropriate in patients over 70 years.

**Subclinical hyperthyroidism**

Subclinical hyperthyroidism is biochemically defined as low serum TSH concentrations (<0.5 mU/ml) with normal serum free T4 and triiodothyronine (T3).

It is caused by either exogenous or endogenous disease. Exogenous disease is more common due to the widespread use of thyroxine for treatment of thyroid disease. Autonomous functionally thyroid adenomas and multinodular goiters are the most common causes of endogenous subclinical hyperthyroidism. Among patients over 55 years, hyperthyroidism due to multinodular goiters was subclinical in 57% of patients, while hyperthyroidism due to Graves’ disease was subclinical in only 6% of patients (5). Subclinical hyperthyroidism can occur in patients with thyroiditis and in patients with early Graves’ disease prior to the onset of more overt hyperthyroidism.

It is more common in females, smokers, elderly and in areas of the world with mild to moderate iodine deficiency (6). Progression to overt hyperthyroidism is uncommon but in patients with large nodular thyroid and subnormal TSH, the development of overt hyperthyroidism may occur after iodine exposure.

**Diagnosis**

If the serum TSH concentration is below normal, the TSH measurement should be repeated along with serum free T4 and T3 to exclude overt hyperthyroidism and T3 toxicosis. The diagnosis is based upon the combination of a low serum TSH and normal serum free T4 and T3.

As the serum TSH concentration can be transiently reduced, a repeat TSH, free T4 and T3, should be performed after 3 to 6 months to confirm the diagnosis.

**Differential diagnosis**

The combination of low serum TSH and normal free T4 and T3 concentrations are seen in three other conditions;

- **Central hypothyroidism** – Some patients with central hypothyroidism have low serum TSH and normal (but usually low or low-normal) free T4 and T3 concentrations.
- **Non-thyroidal illness** – Euthyroid patients with nonthyroidal illness, especially those receiving high-dose corticosteroids or dopamine, may have low serum TSH and low-normal free T4 and T3 concentrations.
- **Recovery from hyperthyroidism** – Serum TSH concentrations may remain low for up to several months after normalization of serum T4 and T3 concentrations in patients treated for hyperthyroidism or recovering from hyperthyroidism caused by thyroiditis.

**Pregnancy**

The diagnosis of true subclinical or overt hyperthyroidism during pregnancy may be difficult because of the changes in thyroid function that occur during normal pregnancy. Transient subclinical hyperthyroidism in the first trimester of pregnancy is considered a normal physiologic finding. True subclinical hyper-
thyroidism may occur, but it is not typically associated with adverse outcomes during pregnancy and does not require therapy (7). Furthermore, in pregnant women with overt hyperthyroidism, the goal of therapy is to maintain serum free T4 concentrations in the high-normal range and serum TSH concentrations in the low-normal or suppressed range (8).

**Evaluation**

Patients with subclinical hyperthyroidism should be questioned about symptoms of hyperthyroidism in addition to a past history of thyroid disease, exposure to iodine containing radiographic contrast media, herbal products or medications that may suppress TSH (T4, high dose corticosteroids). Women of childbearing age should be questioned about the possibility of pregnancy as high hCG in pregnancy can give rise to low TSH. All patients should be examined for the presence of thyroid gland enlargement and nodularity.

In patients who are considered for treatment, it is useful to obtain a radioactive iodine uptake scan to help determine the etiology. For example some patients with subclinical hyperthyroidism due to Graves Disease may remit spontaneously without therapy, so that continued observation without therapy is reasonable. Women of childbearing age should have a negative pregnancy test prior to undergoing radioactive iodine scanning. If the scan shows one or more focal areas of increased uptake, this could account for a toxic solitary or multinodular goiter. In patients with low or no uptake on radioiodine scan, the etiology of subclinical hyperthyroidism may be thyroiditis or recent iodine exposure (9).

In postmenopausal women or other patients at risk of osteoporosis, a bone densometry study is useful in making a decision to treat subclinical hyperthyroidism.

**Management**

There is little data to guide clinical decisions regarding the treatment of patients with endogenous subclinical hyperthyroidism. Potential benefits of treatment with normalization of TSH, include improvement in certain cardiovascular parameters and bone mineral density. However, there are no studies evaluating the long-term benefits of correcting subclinical hyperthyroidism, particularly studies with clinically important endpoints, such as cardiovascular disease and fractures.

The American Thyroid Association divides patients into high risk and low risk categories prior to treatment (8). The recently published clinical guidelines by the Endocrine Society of Sri Lanka recommends treatment as follows (4).

<table>
<thead>
<tr>
<th>Factor</th>
<th>TSH (&lt;0.1 mU/L)</th>
<th>TSH (0.1-0.5 mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 yrs</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Age &lt;65 with comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Hyperthyroid symptoms</td>
<td>Yes</td>
<td>Consider treating</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Age &lt;65, asymptomatic</td>
<td>Consider treating</td>
<td>No</td>
</tr>
<tr>
<td>Toxic nodular goiter</td>
<td>Consider treating</td>
<td>Consider treating</td>
</tr>
</tbody>
</table>

In patients at low risk for complications of hyperthyroidism (young individuals, pre-menopausal women) if the serum TSH value is < 0.1 mU/ml, treatment is undertaken only if the patient has symptoms suggestive of hyperthyroidism, confirmed osteoporosis, cardiovascular disease and a thyroid radionuclide scan showing a toxic nodular goiter. If these features are not present or if the TSH is between 0.1 to 0.5 mU/ml, observation alone is appropriate. TSH, free T4, and T3 must be measured every six months.

During the assessment if patients are found to be osteoporotic or have atrial fibrillation, appropriate treatment with bisphosphonates, calcium and anticoagulation has to be initiated.

**Treatment options**

The treatment options for patients with subclinical hyperthyroidism are the same as those for overt hyperthyroidism and depend upon the underlying etiology. Beta-adrenergic antagonist drugs are useful to control symptoms of adrenergic over activity such as palpitations and tremor.

Most patients with thyroiditis require no treatment since thyroid dysfunction is transient and rarely severe. However, thyroid tests should be monitored until normalization.

For patients who need treatment, radioactive iodine is the preferred mode of therapy, especially for patients with toxic solitary or multinodular goiters. A 12 month course of anti-thyroid drugs can be considered if the etiology is likely due to Graves’ because of high remission rates (9).
References


Seizures: a rare presentation of Sheehan’s syndrome

M S A Cooray1, Uditha Bulugahapitiya2, D D Ranasinghe3


Abstract

Sheehan’s syndrome is a well-known cause of panhypopituitarism following ischemic damage to the pituitary gland or stalk during peripartum period. Degree of hypopituitarism in Sheehan’s syndrome can vary and due to the slow evolution, the diagnosis can be delayed. Here we report a case presented to us with hyponatremia, 2 years after her complicated delivery, which highlights the importance of recognizing hyponatremia as a presentation of hypopituitarism in Sheehan’s syndrome.

Key words: hyponatremia, Sheehan syndrome

Introduction

Sheehan’s syndrome, first described by Sheehan in 1937 (1), is a well-known cause of panhypopituitarism following ischemic damage to the pituitary gland or hypothalamic-pituitary stalk during peripartum period (2) and this is usually due to intrapartum or postpartum hemorrhage with severe hypotension or hemorrhagic shock (Table 1). Vasospasm, thrombosis and vascular compression of the hypophyseal arteries have also been described as possible causes (3). Rarely, it may occur even after a normal uncomplicated delivery without significant amount of bleeding. Although the pathogenesis of Sheehan’s syndrome is not completely clear, widespread ischemia is considered to be the main reason for the impairment of anterior pituitary function. Onset of the disease, degree of hypopituitarism and disease presentation can vary. Here we describe a patient with Sheehan’s syndrome who presented 2 years after the possible ischaemic episode with recurrent convulsions due to severe hyponatraemia.

Case Report

A 39 year old woman has got admitted to a medical casualty unit with generalized tonic clonic convulsions, which had been preceded by altered behaviour, headache and vomiting. Following the seizures, the patient had been drowsy with impaired level of consciousness. While in the ward, she has undergone extensive investigations that included cerebro-spinal fluid (CSF) analysis and CT imaging of the brain, which did not reveal any abnormality. She was treated empirically with intravenous antibiotics, antiviral treatment (Acyclovir) and intravenous steroids for suspected meningitis after which she recovered. During this admission, she was also found to have hyponatremia, which was attributed to syndrome of inappropriate ADH secretion (SIADH) and managed conservatively. She dramatically improved with the course of antibiotics and steroids and on discharge was asymptomatic and well. She was discharged on antiepileptic drugs but following discharge her health lasted for only a few days after which she became confused with severe vomiting and then went on to develop seizures. She was re-admitted to the medical casualty unit several days later with recurrent seizures. The initial response to intravenous anti-epileptic drugs was poor and she was found to be hypotensive and needed fluid resuscitation. Recurrent central nervous system infection was suspected and she was again treated with intravenous steroids and antibiotics. However, the CSF analysis was normal and blood and CSF cultures did not yield any organisms. Her biochemical investigations revealed severe hyponatraemia ranging from 116 to 124

Table 1. Criteria for diagnosis of Sheehan’s syndrome

1. Typical obstetric history of postpartum vaginal bleeding.
2. Severe hypotension or shock for which blood transfusions or fluid replacement was needed.
3. Failure of postpartum lactation.
4. Failure to resume regular menstruation after delivery.
5. Varying degree of anterior pituitary failure (partial or panhypopituitarism).
6. Empty sella on CT or MRI scan of the pituitary.

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mmol/L with marginal hyperkalaemia. She also had haematological evidence of normocytic normochromic anaemia with a haemoglobin of 8.8 g/dl. Her symptoms resolved with the initiation of intravenous steroids and fluid resuscitation and her serum sodium got normalised.

Her past history revealed a pregnancy complicated by pre-eclampsia, 2 years prior to onset of convulsions, for which she underwent an emergency caesarean section. Following delivery, she had developed postpartum haemorrhage with shock, for which she required multiple blood transfusions. Subsequently, she had lactation failure and experienced asthenia and fatigue with loss of appetite and weight. These symptoms were attributed to anaemia and were treated with haematinics. However, she didn’t have any improvement with the symptoms and could not tolerate even a minor illness. Although she had regained menstruation 6 months after the delivery, her sex desire has been less and she was not fertile despite unprotected sexual exposure. She denied a history of polyuria and polydipsia.

Clinical examination revealed sparse pubic and axillary hair with normal adult type external genitalia. Hormonal assays revealed a 9 am cortisol of 2.69 μg/dl (5-25) and post ACTH stimulation cortisol level of 7.9 μg/dl. Her free T4 level was 0.77 ng/dl with a TSH of 1.36 μIU/mL. Her LH, FSH and estradiol levels were 2.08 u/L, 2.38 u/L and 59 pg/mL respectively. Based on these findings, she was diagnosed as having panhypopituitarism. Pituitary imaging with a MRI scan of the pituitary revealed atrophied anterior pituitary, which was compatible with a diagnosis of pituitary infarction (Figure 1) (4).

She was started with pituitary replacement therapy with hydrocortisone and levothyroxine sodium. Her clinical condition, serum sodium and haemoglobin levels improved and reached normal range with hormone replacement.

**Discussion**

Hypothyroidism, adrenal insufficiency, hypogonadism, growth hormone deficiency, hypoprolactinemia, and different sodium and water disturbances are well-described clinical features of Sheehan’s syndrome (3). Enlargement of pituitary gland, small sella size, disseminated intravascular coagulation and autoimmunity have been suggested to play a role in the development of Sheehan’s syndrome in women who suffer from severe postpartum haemorrhage. Although a small percentage of patients with Sheehan’s syndrome may present with severe hypopituitarism immediately after delivery, majority have mild disease and go undiagnosed and untreated for years. It may result in partial or panhypopituitarism and the great majority of the patients have empty sella on CT or MRI scan of the pituitary (4).

Lack of lactation and failure of menstrual resumption after a delivery are the most important clues to the diagnosis of Sheehan’s syndrome (5). Although our patient had lactation failure, she continued to have menstrual cycles until presentation, which may have probably delayed the diagnosis of hypopituitarism. Gonadotrophic function may be preserved in an occasional patient. There have been several reports of patients with Sheehan’s syndrome who maintained regular menstrual cycles and even became pregnant spontaneously (7-9). Thus, the absence of amenorrhea or the presence of postpartum lactation, does not rule out the diagnosis.

The occurrence of sodium and water disturbances associated with Sheehan’s syndrome depends on the degree of pituitary damage, time of onset since the initial pituitary insult, and concurrent medical conditions (6). Hyponatremia is not a disease, but a manifestation of a variety of disorders and it may be the only manifestation of hypopituitarism or hypothyroidism. The diagnosis of hypopituitarism in hyponatraemic patients is often overlooked and it is a common electrolytic disorder, occurring in 33% to 69% of all cases with Sheehan’s syndrome (10).

Several mechanisms are responsible for hyponatremia in patients with Sheehan’s syndrome. Hypothyroidism and glucocorticoid deficiency by decreasing free water clearance independent of vasopressin cause hyponatremia. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and volume depletion can also lead to hyponatremia. Volume depletion, cortisol deficiency and hypothyroidism are the causative factors for hypo-
natraemia in our patient and this was easily corrected with salt replacement with hydrocortisone and thyroxine treatment (10-13).

Panhypopituitarism is often accompanied by normocytic normochromic anaemia, which is usually mild and seldom below 9 g/dL. This is due to cortisol deficiency, hypothyroidism and hypogonadism. It has shown that glucocorticoids stimulate erythropoiesis and thyroid hormone stimulates erythropoietin production and proliferation of erythroid progenitor cells (2). Our patient’s haemoglobin level improved with adequate cortisol and thyroxine replacement.

Although Sheehan’s syndrome is uncommon as a result of improved obstetric care, it should be a consideration in any woman who has a history of a postpartum hemorrhage and who reports signs or symptoms of pituitary deficiency. Replacement of deficient hormones is important not only to correct endocrine abnormalities, but also to reduce mortality due to hypopituitarism (5). In patients who have secondary hypothyroidism and hypocortisolism, glucocorticoids should be replaced before the replacement of thyroid hormone. Gonadotropin deficiency and hypogonadism should be treated with hormone replacement therapy.

This case highlights the importance of identifying hyponatraemia as a presentation of hypopituitarism and the possibility of Sheehan’s syndrome when presented after childbirth especially with vague and varied clinical features, even if all pituitary axes seem to be unaffected.

References

A young patient with severe virilization, hypertension and bilateral adrenal hyperplasia

S A Abhayaratna¹, N P Somasundaram²

Abstract

We describe an unusual late presentation of 11β-hydroxylase deficiency in a severely virilized, 23 year old patient, who presented with intracerebral haemorrhage, hypertension and short stature. The patient was raised as a male but had hypospadias, absent testicles from birth and had precocious puberty during his childhood. Plasma testosterone level was elevated (16 ng/mL) with suppressed FSH and LH levels (< 1 U/L). Basal 17-hydroxyprogesterone was markedly elevated (>19.2 ng/mL-ref range: 0.5-2.1 ng/mL). CT scan abdomen showed bilateral marked adrenal hyperplasia with mullerian structures and karyotyping showed 46 XX with negative sex-determining region Y (SRY) test. A clinical diagnosis of 11β-hydroxylation deficiency was made in view of hypertension with severe virilization in a 46 XX individual. The patient was managed with antihypertensive drugs, monitoring of serum testosterone and 17-hydroxyprogesterone levels since she the patient decided to remain as a male.

Key words: congenital adrenal hyperplasia, 11-β-hydroxylase deficiency.

Introduction

Congenital adrenal hyperplasia (CAH) is a family of disorders, with an autosomal recessive inheritance, characterized by enzymatic defects in one of the steps in cortisol production. Steroid 11β-hydroxylase deficiency is the second most common cause of CAH, accounting for 5-8% of all cases (1, 2). It is caused by the mutation of the CYP11B1 gene that encodes the enzyme. In classical 11β-hydroxylase deficiency, mutations of the CYP11B1 gene result in decreased activity or inactivation of the enzyme (3). Deficiency of 11β-hydroxylation causes a decrease in conversion of 11-deoxycorticosterone to cortisol and 11-deoxycortisol to cortisol. (Figure 1). Reduced cortisol feedback gives rise to an increase in adrenocorticotropic hormone (ACTH) secretion, which stimulates increased production of 11-deoxycorticosterone and 11-deoxycortisol.

![Figure 1. Adrenal steroid synthesis. Deficiency in 11β-hydroxylase (CYP11B1) results in accumulation of DOC and consequent hypertension; increased androgen synthesis.](image)

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Case report

A 23 year old male patient was admitted to the neurosurgical ward with sudden onset altered consciousness, difficulty in speech and right sided face-arm-leg weakness. The patient was found to have hypertension on admission (blood pressure 240/130 mmHg). A computerized tomography (CT) scan of the brain showed left sided intracerebral haemorrhage with cerebral oedema. He was transferred to the neurosurgical intensive care unit (ICU) and blood pressure was controlled with antihypertensive drugs and intravenous dexamethazone was administered for cerebral oedema. He underwent a four vessel digital subtraction angiography which was found to be normal. His condition gradually improved in the ICU and blood pressure was controlled with losartan 50 mg twice daily and was transferred to the neurosurgical ward. During further examination in the ward he was found to have bilateral absent testicles and hypospadias apart from his short stature. His routine investigations showed mild persistent hypokalaemia (despite treatment with losartan), hypertensive heart disease and bilateral adrenal masses on ultrasound scan of the abdomen (right side: 4 cm × 3.5 cm, left side: 2.5 cm × 2 cm). The patient was referred for endocrine opinion and a detailed history revealed that he was assigned male sex at birth but had absent testes at the neonatal examination. However, the parent’s defaulted clinic follow up. By the age of five years he was found to be taller then most of his peers and around the same time he developed deepening of voice, axillary and facial hair. He stopped gaining height since then and by the age of 10 years he was shorter than most of his peers. At this point, parents sought medical advice and after investigations (including karyotype analysis), he was informed to be of “female gender”. Parents could not accept raising this child as a female and the child was lost to follow-up until he presented to us at the age of 23 years with hypertension induced cerebral hemorrhage. There was no family history of similar disease. He was 145 cm tall (well below 3rd percentile) and pigmented. His pubic hair was of Tanner stage IV, with a phallus of 6.5 cm in length and penile hypospadias. The scrotal sac was empty and testes were not palpable in the inguinal area. Blood pressure was 160/100 mmHg with grade three hypertensive retinopathy. There were no palpable masses or renal bruits in the abdomen and there was no gynaecomastia.

His plasma testosterone level was elevated (>16 ng/mL) with suppressed FSH and LH levels (< 1 U/L). Basal 17-hydroxyprogesterone was markedly elevated (>19.2 ng/mL - ref range: 0.5-2.1 ng/mL). 11-deoxycortisol levels could not be performed due to unavailability of the test. CT scan abdomen showed bilateral marked adrenal hyperplasia with presence of mullerian structures (Figure 2) and

Figure 2 A and B – Bilateral adrenal hyperplasia (white arrows), C-Mullarian structures (grey arrow).
A young patient with severe virilization, hypertension and bilateral adrenal hyperplasia

karyotyping showed 46 XX with negative SRY. A diagnosis of 11β-hydroxylase deficiency was made in view of hypertension with severe virilization in a 46 XX individual. However the serum cortisol level in this patient was elevated (1232 and 868 nmol/L) with unsuppressed overnight dexamethasone suppression test (ODST 102 nmol/L). Dehydroepiandrosterone sulfate level was also within the normal range (136 μg/dL -95% reference range: 35-430 μg/dl). His urinary vanillylmandelic acid (VMA) level was 9.6 mg/24 hrs. (Ref: 1-11 mg/24 hrs.) After psychological counseling and education of the patient and the family, he chose to remain as a male. He was treated with nifedipine slow releasing tablet 20 mg twice daily, low sodium diet to control hypertension, physiotherapy and speech therapy to improve motor skills and speech. Steroids, which are the mainstay of treatment in CAH, were not started initially due to the negative effect they would have on androgen production and hence his male characteristics. However, he was advised to use steroids in stress situations and close monitoring with testosterone levels and 17-hydroxyprogesterone levels were planned on follow up visits. It was decided to start a long acting steroid if testosterone level remains markedly elevated during follow up. Urological referral was done in view of genital reconstruction and removal of mullerian structures once there is reasonable recovery from stroke.

Discussion

In CAH due to 11β hydroxylase deficiency, development of the female external genitalia is affected in utero by excess fetal adrenal androgens, resulting in genitalia which are ambiguous. Most females with the severe or classical form of CAH are diagnosed in the neonatal period after presenting with ambiguous genitalia at birth or in early childhood. Occasionally, females are so severely virilized at birth that their external genitalia are male looking, with a penile urethra and fused labioscrotal folds (4). This leads to errors in gender assignment as in our patient. Due to delay in diagnosis in this patient, he was raised as a boy and didn’t attend any regular medical follow up as he was seen as a normal male externally. The time which the initial diagnosis was suspected was too late for his parents to accept a new gender and he was lost to follow up. It has been shown that early diagnosis and treatment of CAH in a severely virilized female allows better psychological adjustment apart from preserving fertility (5). If the diagnosis is late, it is a dilemma whether to change the gender because of possible female fertility or to remove the female organs and continue to rear the child as a male. The decision depends on the age at diagnosis and the cultural context. Typical signs of androgen excess include masculinization of female external genitalia and precocious pseudopuberty in both sexes. Patients undergo rapid somatic growth with premature epiphyseal closure resulting in short adult stature. Elevated metabolites with mineralocorticoid activity, such as deoxycorticosterone and its derivatives, cause hypertension in about two thirds of patients (4, 6).

Biochemical profile and imaging suggested that CAH with 11β-hydroxylase deficiency is the most likely diagnosis in this patient. Generally in CAH patients, low cortisol levels increase ACTH production, flooding the adrenal steroidogenic machinery with upstream precursors (4). However in this patient cortisol levels were persistently elevated with non-suppressed levels following dexamethasone. Since other features were compatible with the diagnosis, this prompted us to think of an interference with the cortisol assay. Measurement of cortisol by immunoassay is compromised by the potential for cross-reactivity of reagent antibodies with structurally-related steroid compounds present in patient’s serum (7). The elevated levels of cortisol in this patient was probably due to the elevated 11-deoxy cortisol levels cross reacting with the radioimmunoassay technique used in the estimation of cortisol level. Usually DHEAS is elevated in CAH, but some times there is only mild elevation and it is not a consistent feature (8). In our patient DHEAS level was within normal limits.

In this patient, abdominal imaging revealed preserved mullerian structures. Unlike the external genitalia, gonads and internal structures (ovarian tubes, uterus and cervix) that are derivatives of the Mullerian ducts are preserved since the substance that normally causes involution of these structures in men (mullerian inhibiting factor) is not produced by the foetal ovary (9).

Management of CAH due to 11β hydroxylase deficiency comprises glucocorticoid administration to provide cortisol replacement and to normalize ACTH, which in turn removes the drive for over secretion of deoxycorticosterone and in most cases brings about remission of hypertension. Patients with 11β-hydroxylase deficiency cannot mount a sufficient stress response and should receive appropriate stress doses of glucocorticoids as for other patients with adrenal insufficiency (4). In our patient, he and the family decided that he would remain as a male. The main challenge in this situation was to keep the androgen level to maintain his male characteristics and to control the hypertension. His blood pressure was controlled with nifedipine SR 20 mg twice daily dose. It was decided not to start steroids initially as it would unmask his female characteristics such as regression of facial hair, male pattern of body hair, change of voice and initiation of menstrual periods which would present as urethral bleeding. It was targeted to keep the testosterone levels in the high normal range with regular monitoring. Steroid treatment was planned if the blood pressure control proves to be difficult or if the testosterone levels keep markedly elevated. Potassium-sparing diuretics, such as spironolactone is effective in controlling hypertension due to mineralocorticoid excess in 11β hydroxylase deficiency. Spironolactone has antiandrogenic properties and would have unmasked the above mentioned female characteristics in our patient. His blood pressure was also adequately controlled with nifedipine and lifestyle
modifications. Due to those reasons it was not started in our patient.

The patient was referred to the psychiatric unit for further counseling and he was explained about lack of fertility. Genitourinary referral was done for the correction of hypospadias and for the removal of Mullerian structures. He gained slow but steady recovery from his limb weakness with continued physiotherapy.

Apart from karyotype analysis, DNA analysis is used routinely in some countries where common mutations have been identified. 11β-hydroxylase deficiency can now be diagnosed prenatally by measuring tetrahydro-11-deoxycortisol in amniotic fluid (10). If one child in a family is already affected by congenital adrenal hyperplasia, prenatal diagnosis during pregnancy should be offered (11). In addition to enabling genetic counselling, prenatal diagnosis offers the opportunity to consider prenatal treatment with dexamethasone in order to prevent virilization of the external genitalia of XX fetuses (12). These genetic investigations are not available in the country.

Due to lack of availability, we were unable to perform plasma levels of 11-deoxycortisol and renin which would have conclusively proven the diagnosis, but as described earlier clinical and available biochemical results supported the diagnosis of CAH due to 11β-hydroxylase deficiency. Although ACTH dependent Cushing syndrome is a cause of bilateral adrenal hyperplasia especially when cortisol levels are high, lack of clinical features of Cushing syndrome and the overall clinical and biochemical picture with ambiguous genitalia was more in favour of CAH. Consistent with this diagnosis, ACTH level was thought to be high in this patient as evident by the body pigmentation. Biochemical measurement of ACTH was not undertaken due to unavailability at the time. Magnetic resonance imaging (MRI) of brain, to exclude an ACTH secreting pituitary adenoma was also not performed as it was not readily available and CAH was the most likely diagnosis.

Conclusion

We report this case to show the importance of early diagnosis, explanation and treatment in conditions which cause ambiguous genitalia in newborns including CAH. Late diagnosis leads to gender reassignment at a age which is not acceptable to many patients and families causing psychological distress, loss of follow up and patients eventually present with complications of the disease. Patients and families need adequate psychological and social support and side effects of treatment should be monitored carefully.

References

**Differential diagnoses of hyperandrogenism in a post menopausal woman**

K Dharshini¹, Uditha Bulugahapitiya²

*Sri Lanka Journal of Diabetes, Endocrinology and Metabolism 2013; 3: 95-97*

**Abstract**

Evaluation of postmenopausal women with hyperandrogenism should be focused to identify the underlying pathology. Clinicians should have high degree of suspicion. The spectrum of differential diagnoses could be more sinister causes like androgen secreting adrenal and ovarian tumours in one end and the polycystic ovarian syndrome in the other end. We describe a postmenopausal woman who presented with hyperandrogenism due to Sertoli-Leydig cell tumour of the ovary. Her testosterone levels returned to normal four weeks after surgery.

**Key words:** post menopause, hyperandrogenism, Sertoli-Leydig cell, ovarian tumour.

**Introduction**

The clinical presentation of hyperandrogenism in postmenopausal women may be atypical and late, because disturbance in the menstrual cycle and pattern of hair growth could be attributed to normal aging. Evaluation should be focused to identify the possible underlying pathology. Although rare, ovarian and adrenal tumours should be considered in the differential diagnoses, as early detection has good prognosis.

**Case report**

A 58 year old postmenopausal woman was referred to us with a history of increased facial and body hair for one year duration and deepening of voice for 3 years. Her menstrual periods had been regular until she reached menopause at the age of 47 years. Her medical history was notable for hypertension diagnosed 4 years ago and osteosarcoma of left tibia and surgical above knee amputation 18 years ago. She was a mother of two children and denied having a family history of hirsutism or androgenic disorders.

On physical examination, she had male pattern frontotemporal balding and hirsutism (Figure 1). Regular hair removal made difficulties in scoring the severity of hirsutism. Pelvic examination showed no palpable masses or clitoromegaly.

She had elevated levels of serum total testosterone with 3.82 ng/ml (normal range 0.15 to 0.81). Her follicle-stimulating hormone (FSH) and luteinizing hormone (LH) values were 28.4 and 32IU/L respectively compatible with postmenopausal state. She had normal levels of dehydroepiandrosterone sulfate (DHEAS) which was 17.5 μg/ml (3.5 - 43). Her 17β-hydroxyprogesterone was also within normal range, 0.46 ng/ml. She had normal cortisol response to overnight dexamethazone suppression test. Her testosterone level was not suppressed with low dose dexamethazone suppression test. This indicates possible ovarian source for her hyperandrogenism, since more than 40% suppression would be expected if it is from adrenal source. Transvaginal ultrasonography revealed an enlarged right ovary. A computed tomographic scan of the abdomen and pelvis showed normal adrenal glands and an ill defined mass in right adenexial area.

Since both biochemical and imaging studies localized the source of the hyperandrogenism to ovaries, the patient was offered hysterectomy and bilateral salpingo oophorectomy. Intra-operatively the right ovary was enlarged without any adhesions to surrounding structures (Figure 2). Histology confirmed intermediate differentiated sertoli-Leydig cell tumour of right ovary. Four weeks post operatively her serum testosterone returned to normal levels.

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Case report

Discussion

This case describes a post menopausal female who presented with hyperandrogenism due to sertoli-leydig cell tumour of ovary. This tumour is a rare ovarian tumour often detected in young women and very rare in post menopausal age. Therefore clinicians should consider all potential underlying causes of hyperandrogenism when postmenopausal women presented with hirsuitism. Currently the literature is sparse concerning the long term effects of hyperandrogenism in menopausal women. Nevertheless the recent reports indicate association between high androgens and several metabolic derangements. These includes altered lipids (1), insulin resistance, obesity, diabetes (2), advanced glycation end products (3), fluid retention, elevation in haematocrit and hypertension (4), as well as high risk for breast cancer (5) and cardiovascular disease (2). To prevent these long term negative health consequences androgen excess should be detected and treated appropriately.

The possible differential diagnoses are summarized in Table 1. Poly cystic ovarian syndrome (PCOS) is a most common cause for hyperandrogenism in premenopausal women. As there is no sharp decline in ovarian testosterone production during menopause, late diagnosis of PCOS is not a rare entity (6,7). Hyperthecosis, a severe form of PCOS due to overproduction of androgens by ovarian stromal cells as a result of high levels of gonadotrophines in postmenopausal women also need to be considered (8). Obesity induced hyperandrogenism, an entity where signs of hyperandrogenism develop with weight gain. Women will have cystic ovaries without elevated LH/FSH ratio. The excessive local production of oestrogens and androgens by surplus aromatase and 5 alpha reductase activity in adipose tissue is the possible mechanism (7).

Table 1. Differential diagnoses of postmenopausal hyperandrogenism

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Clinical clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycystic ovarian syndrome</td>
<td>Long duration and features of hyperandrogenism prior to menopause.</td>
</tr>
<tr>
<td>Ovarian hyperthecosis</td>
<td>Long history, more severe hirsuitism and virilization.</td>
</tr>
<tr>
<td>Obesity induced hyperandrogenism</td>
<td>Timing of hyperandrogenism correlate with weight gain and symptoms reverse with weight loss.</td>
</tr>
<tr>
<td>Androgen secreting ovarian or adrenal tumours</td>
<td>Rapidly onset, more severe hyperandrogenism.</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Cushingoid features</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Medications such as DHEA supplements and exposure to male partners’ testosterone gel.</td>
</tr>
</tbody>
</table>

Ovarian or adrenal tumours produce high levels of androgens and patients usually present with virilization of short duration (9). Adrenal tumours secreting DHEA, DHEAS and rarely testosterone, will cause hyperandrogenic picture and patients with adrenal carcinoma will have high levels of DHEAS (10).

Androgen producing ovarian tumours include sertoli cell and leydig cell tumours, steroid cell tumours not otherwise specified and ovarian thecoma (11). Sertoli-Leydig cell tumours constitute less than 0.5% of ovarian tumours. Depending on the differentation, it behaves as benign or malignant fashion (12). Steroid cell tumours account for 0.1% of ovarian tumours. These are usually
benign with relatively long history of androgenic changes (13). Ovarian thecoma is typically present in older women with majority in postmenopausal period. These account for 0.5 to 1% and they mainly secrete oestrogen. But they are virilizing in 10% (14).

Therapeutic options for post menopausal women with hyperandrogenism depend on the aetiology. Surgical cure for adrenal and ovarian tumors, with total hysterectomy and bilateral oophorectomy is a suitable surgical option in post menopausal females with ovarian tumours as in our patient (13). Whereas in young women unilateral oophorectomy is desired and patients can avoid exogenous hormone replacement (15, 16). Although there is no standard regime, for patients with malignant sertoli-leydig cell tumours platinum based adjuvant chemotherapy is recommended following surgery (17).

Conclusion

This case illustrates the rare possibility of Sertoli-Leydig cell tumour of ovary in a postmenopausal woman with hyperandrogenism. She had a relatively long history of symptoms, though androgen producing ovarian tumours typically have rapid onset of symptoms. This explains the importance of high degree of clinical suspicion when evaluating older women with hirsuitism.

References

Ectopic thyroid tissue presenting as a cardiac mass

Steven Henderson¹, Adam Din², Wael Elsaify³


Abstract

Thyroid ectopia is a rare, congenital phenomenon. Ectopic thyroid tissue located within the heart is extremely rare, with less than 30 cases ever reported. We present one such case with, what we believe, is a unique presentation.

A 46 year old woman presented with chest pain. Echocardiogram demonstrated a right ventricular mass which was later excised and found to be thyroid tissue. Multiple investigations failed to demonstrate any further abnormality and a diagnosis of intra-cardiac thyroid ectopia was made.

A variety of embryological abnormalities can lead to thyroid ectopia and it is linked to several genetic mutations. Interruption of thyroid migration can lead to thyroid tissue being deposited anywhere along its path. Before the diagnosis of ectopia is made, however, thyroid malignancy must first be excluded. Other differential diagnoses include struma ovarii and malignant emboli. Although exceptionally rare, intra-cardiac thyroid ectopia should be considered for any unusual cardiac mass prior to invasive treatment or investigation.

Key words: thyroid, ectopia, cardiac.

Introduction

Primary cardiac tumours are rare, usually benign lesions with an overall incidence of 0.05-0.5% (1,2). The most common form of primary cardiac tumour, accounting for 25% of cases, is a myxoma, a pedunculated tumour arising from the endocardium (3). More commonly, cardiac tumours are metastatic deposits, although these are still rare with an incidence of less than 1% of cancer patients (1).

Thyroid ectopia is defined as thyroid tissue at any site other than anterolateral to tracheal rings 2-4 (1,4,5). Again, it is a rare congenital phenomenon occurring in 1 per 100,000-300,000 of the general population (5). Ectopic intra cardiac thyroid tissue is rarer still, with less than 30 cases reported worldwide in the literature since it was first described in 1941 by Dosch (6-9).

Despite this, it is an important differential in the diagnosis of a cardiac mass. We present one such case in which the patient presented with chest pain followed by a brief review of the available literature.

Case report

A 46 year old woman, with a background of non-insulin dependent diabetes, presented with an 8 week history of left sided chest pain. The pain was dull in nature, did not radiate and had no other associated features. It was not related to exercise and, by the time of her presentation, was occurring daily. She had previously undergone hysterectomy and appendicectomy. There was no family history of note and she was a lifelong smoker.

In the first instance, an ECG and echocardiogram were arranged. The ECG showed normal sinus rhythm with no evidence of ischaemic injury. The echocardiogram demonstrated a 2.6 × 1.6 cm right ventricular mass (Figure 1). Ventricular size and function were normal and there was no valve dysfunction. Subsequent CT pulmonary angiogram did not demonstrate any pulmonary lesions although an incidental left breast fibroadenoma was detected. Completion CT abdomen and pelvis showed no other lesion. The ovaries were noted to be cystic and the thyroid was unremarkable. A bone scan was also reported as normal. Prior to surgery, the patient underwent coronary angiogram which demonstrated only mild disease of the

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left anterior descending artery (LAD). The mass in the right ventricle derived its blood supply from the septal branch of the LAD.

The thyroid is connected to the pharyngeal floor by the thyroglossal duct in the early stages of development but this normally disappears by week 10. The thyroid descends along the path of the thyroglossal duct in front of the trachea, anterior to the hyoid bone and thyroid cartilage, to its final pre-tracheal position in gestational week 7 (1,5,10). Interruption of this descent is the most common cause for thyroid ectopia (13). As a result, lingual thyroid is the most frequent, occurring in 90% of cases. Suprahyoid, infrayoid, submandibular, tracheal, lateral cervical, axillary, palatine tonsils and the bifurcation of the carotid artery are all locations in the head and neck region that have been reported to contain ectopic thyroid tissue (2,5). Ectopic thyroid tissue has also been reported at more distant sites in the liver, duodenum, jejunum, pancreas, porta hepatitis, gallbladder, stomach, adrenal gland, aorta and oesophagus (4,5,10) explained, most likely, by over-descent of the thyroid during embryogenesis.

Several genetic mutations are postulated to be associated with thyroid ectopia. Tiffl, Foxe1, Pax 8, Hhex and Tshr are required for the normal development of the thyroid gland. Animal studies have suggested that genetic abnormalities in these genes could be associated with abnormal thyroid development and possible thyroid ectopia (5,14).

Once the presence of thyroid tissue is confirmed in the cardiac tissue, it is important to exclude metastatic follicular carcinoma. Thyroid carcinoma metastasising to the heart is rare, occurring in less than 1% of cases (1,9). Metastatic thrombi from a primary thyroid cancer can be deposited in the heart via the thyroid veins (9).

Struma ovarii, another important differential, is an ovarian teratoma that consists of mature thyroid epithelium (15,16). 15% of cases of struma ovarii may manifest hyperthyroid features and, importantly, up to 5% may develop carcinoma (15).

The clinical presentation of cardiac tumours is often non-specific and usually does not cause symptoms until cardiac function is impaired (1,6). Palpitations/arrhythmias, dizzy spells, conduction defects and emboli can, however, be features (1,6,8,9,12). We believe our patient to be the first to present with isolated chest pain.

Cardiac masses are most commonly identified on an echocardiogram. Once the presence of a cardiac mass is confirmed, further investigation with CT or MRI is common (1,2,7). Coronary angiography will identify the blood supply to the tumour and help with surgical planning (1). Overall, the available literature reports generally good results from surgical resection (7,10,13). Once the mass is identified as thyroid tissue, the thyroid must be investigated for evidence of primary malignancy.
Case report

It is important to note that, as ectopic thyroid tissue contains mature thyroid epithelium, it can produce thyrotoxicosis and can be a source of a primary thyroid carcinoma (5).

Conclusion

Ectopic, intracardiac thyroid tissue is a rare cause of a cardiac mass. It is vital that metastatic thyroid carcinoma is excluded following confirmation of intracardiac thyroid tissue.

References

Selecting the correct research method

Sarath Lekamwasam


There are many methods or designs available for researches when conducting research. Same research question or hypothesis can be tested by different methods but the validity and applicability of results vary. Selecting the most appropriate research method to test the research question is an impotent and critical step in conducting a research.

Research methods, broadly, are of two types; observational and interventional. In each method there are two key elements; Exposure and Outcome. “Exposure” refers to the situation that investigator believes may have caused or may lead to the condition or disease in question (such as smoking or taking a drug). The word “Outcome” denotes the end result, i.e. the clinical condition or disease in question. Most studies basically examine the relationship between the exposure and the outcome. In addition, it can determine the direction and the strength of the relationship too.

The fundamental difference between observational and interventional studies is related to exposure. In observational studies researcher or investigator does not determine the exposure. He has no role to play in determining who would get exposed, the dose or duration of the exposure (e.g. smoking and alcohol consumption). In interventional studies investigator determines the types of people who would get the exposure, dose and duration (e.g. drug trial). As investigator does not determine the exposure it is relatively easy to get ethical approval for the observational studies. In interventional studies the investigator has to justify the exposure and other things related to it such as dose and duration and finally convince the authorities.

**Study designs**

1) Observational
   a. Cohorts
   b. Case control
   c. Cross sectional
2) Intervventional (experimental)
   a. Clinical trials
   b. Community trials

All study designs are not of same quality and they can be arranged in hierarchical manner (Figure 1). Designs in the top of the pyramid generate more valid information than those at the bottom. This is mainly due to the confounders and various forms of biases associated with the study designs at the bottom of the pyramid. Study designs at the top of the pyramid such as clinical trials make maximum effort to eliminate confounders and biases that can compromise the validity of the results.

![Figure 1. Hierarchical arrangement of research designs.](image)

Case histories and case series, although not pure research, have generated valuable and clinically relevant information in the past. There are numerous landmark case histories that have prompted clinicians to think differently, pay more attention to changing disease patterns and inform about rare but serious adverse effects of drugs.

**Cohort studies**

Cohort studies recruit subjects based on the exposure and they are followed up until the desired outcome is manifested. As exposure and outcome are chronologically separated (no outcome at the time of recruitment) the association between them can be easily understood.

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CME

Examples

1) Recruit all males in a town and separate them according to smoking habits and follow them up to detect the occurrence of bronchial carcinoma.

2) Recruit all women with first pregnancy in the first trimester in one MOH area and separate them according to body iron status and follow up to determine the birth weight of newborns.

Cohort studies have an advantage that multiple outcomes can be assessed. e.g. in addition to bronchial carcinoma in the 1st example, one can detect the occurrence of ischemic heart disease and bladder carcinoma etc. The major setback of the design is the period of follow up that may be required in some instances. Malignancies and myocardial ischemia may need several years (or decades) of exposure and study may require long period of follow up. This makes the study expensive, requires more time of the investigator and leads to more drop outs. People may change the residence or lose the interest of the study and may no longer available. Studies of shorter duration such as one described in the 2nd example eliminate some of these practical issues.

Despite all practical limitations cohort studies have contributed to the medical field enormously. Clear examples include Framingham and Rotterdam studies.

Case control studies

In contrast to cohort studies, case control studies recruit subjects based on the outcome. Cases are the subjects with the manifested outcome and they need to be matched with a group of subjects without the outcome. Once the two groups are found, investigator inquires about the exposure in all subjects.

Main advantage of the case control design is that it provides an opportunity to study the association between the exposure and outcome when they are separated by a long time gap (smoking and bronchial carcinoma in the 1st e.g.). One setback of the design is the limitations in recall of events that occurred long time ago. This, however, is common to both groups and may not cause a huge discrepancy of data in the two groups. More serious concern is what is known as the recall bias where one group may recall events better than the other group. In the 2nd example, mothers who had abnormal babies may have spent lot of time reflecting on events that took place during the pregnancy but mothers who had normal babies may not have thought about this at any time. This leads to discrepancy of data in the two groups and can be a serious problem.

Case control studies are relatively cheap and take less time when compared with cohort studies. Also they allow the investigator to examine multiple exposures in one outcome. In bronchial carcinoma the investigator gets a chance to inquire about exposure to industrial dust and type of job in addition to smoking habits. Case control design is an ideal research method to study rare conditions such as congenital anomalies.

Selection of cases needs to be done carefully. One has to decide on case definition. If available, internationally accepted definitions are valuable and should be used (e.g. ACR criteria for SLE). If no such definition can be found, a clinically acceptable definition should be used. Results of a study can be of no interest simply due to poor case definition.

Equal importance should be given to the selection of controls. Controls need to be matched to resemble cases and sufficient care should be taken to exclude the presence of the particular disease under consideration. This can be difficult at times as asymptomatic patients may not like to undergo complicated and invasive procedures such as endoscopies and treadmill exercises. Furthermore, the type of control is also important. Controls can be selected from patients visiting hospitals (Hospital based controls), from neighborhood (Neighborhood controls) and community (Community controls) etc. The investigator must decide on the type of control suitable for his study.

Odd ratio (OR) is the usual statistics used in case control studies. It indicates the type of association existing between the outcome and exposure. OR of 1 indicates the lack of association between the two variables and values greater than 1 are considered risk factors. In contrast, values lesser than 1 are considered protective factors. OR is generally given with the 95% Confidence Intervals and this is required to decide whether the estimate is statistically significant.

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Cross sectional design

In this design, the investigator measures the exposure and outcome, both, in the same sitting.

**Examples**

1) Investigator measures BMI and the severity of knee osteoarthritis among postmenopausal women attending a rheumatology clinic.

2) Investigator measures FEV1 and mobility (Timed Get up and Go Test) of elderly women in a selected MOH area.

Cross sectional studies are relatively easy, cheap and consume less time when compared with cohort studies. Furthermore, no “missing data” should be found as the exposure and outcome are measured simultaneously. However, there are significant drawbacks in this study type.

It may not be possible to establish the causal relationship between the two variables measured in the study as one will not be able to tell the temporal relationship between the two. In the 1st example, it will be difficult to find out whether high BMI caused knee osteoarthritis or knee osteoarthritis caused less mobility and then high BMI.

Clinical trials

Clinical trials are conducted to estimate the effect of a chosen drug, procedure or life style intervention on the outcome of a disease. Unlike in observational studies, in clinical trials the investigator determines the type of the drug, procedure or intervention, dose and duration. In addition, type of monitoring and care during the study period are determined by the investigator. Clinical trials mostly have only two groups of subjects and one group receives the test medication while other group is kept as the control group. The type of care given to the control group has to be determined by the investigator. Most of the time they are given a placebo drug which resembles the test drug (Figure 2).

![Figure 2. Study design of a clinical trial with two parallel groups.](image)

**Examples**

1) Patients with congestive cardiac failure are randomized to two groups and one group is given spironolactone in addition to the standard care. The other group is given a matching placebo in addition to the standard care. The investigator then counts the number of cardiac deaths that occur during the next two years in the two groups.

2) People with impaired fasting glucose are divided to two groups and one group is given intensive physical exercise program to follow and the other group is asked to follow a simple exercise program. The investigator then finds out the occurrence of diabetes in the two groups.

There are few key procedures to follow in clinical trials. They are done to eliminate various forms of biases and confounders that can compromise the validity of results. Randomisation of eligible subjects to study groups is one such step. Randomisation allows equal chances for all subjects to get into any group of the study, hence eliminates selection bias. More importantly, randomization ensures equal distribution of confounding factors between groups. If properly done, randomization helps to achieve prognostically similar study groups.

Blinding is the other key factor. Blinding makes the people concerned unaware of the type of care given to study subjects. Studies can be of Single-blind type where only patients are unaware of the type of care given to them. In Double-blind studies both patients as well as researchers are unaware of the type of care given to study subjects. In addition there are critical groups that need to be blinded. They include parents (in paediatric studies), clinicians, data collectors and statisticians.

Summary

There are many study designs available for researches and the selection of the most suitable method is the first step in conducting a good research. Other key areas that ensure the validity of research outcome include proper selection of cases and controls and elimination of various forms of biases and confounders.

**Suggested further reading**


HbA1C and diabetes – an overview

S Pathmanathan1, Noel P Somasundaram2


Abstract

The hemoglobin A1C (HbA1C) assay has become the gold-standard measurement of chronic glycaemia for over two decades. It provides an average blood glucose level during the preceding 10 - 12 weeks. Its close association with risk for long-term complications, established in epidemiologic studies and clinical trials, has resulted in clinicians using HbA1C test results to guide their treatment decisions, and thus the assay has become the cornerstone of clinical practice. This brief review describes some important facts about HbA1C and its relevance and usefulness in clinical practice.

Introduction

Diabetes has been diagnosed for decades with the measurement of plasma glucose, either fasting (FPG) or post prandial (PPG) assessment or, much less frequently, with an oral glucose tolerance test (OGTT) (1). Fasting and 2-h OGTT only reflect the glucose level at a given moment of a single day and is not good in describing a chronic and complex clinical condition. The hemoglobin A1C (HbA1C) measurement, a biochemical parameter which could reflect hyperglycemia over a long period is more appropriate than a parameter describing it in the short term or in a given moment only (2,3). Today the HbA1C assay is widely accepted and used as the most reliable means of assessing chronic glycaemia and has become the cornerstone for the assessment of diabetes care.

HbA1C – an indicator of chronic glycaemia

It has been shown that HbA1C provides an average blood glucose level during preceding 10 - 12 weeks. But HbA1C truly does not reflect glycemic control over last three months as claimed. Rather, it is weighted to more recent weeks. The average glycaemia during the month preceding the HbA1C measurement contributes 50% of the result, during the 30-60 days prior to the HbA1C measurement contributes another 25%, and during the 60-120 days prior to the measurement contributes the final 25% (4).

The fasting blood glucose as well as post meal glucose excursions contribute to HbA1C levels. Post meal blood glucose contributes significantly when HbA1C is <7.5%. On the other hand, fasting blood glucose contributes more when HbA1C is >7.5% (5).

Diagnosing diabetes with HbA1C

The close association of HbA1C with risk for long-term complications has been well established in epidemiologic studies and clinical trials. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated conclusively that risks for complications are related directly to glycemic control, as measured by HbA1C (6,7). DCCT study documented that maintaining lower blood glucose concentrations (assessed by HbA1C) resulted in a delayed onset and reduced the rate of progression of microvascular complications. Analogous to the DCCT, the UKPDS showed that intensive blood glucose control reduced the risk of microvascular complications. Both the UKPDS and DCCT documented that a small change in HbA1C values translates into a large alteration in the risk of diabetes complications in patients with type 1 or type 2 diabetes (6, 7).

This has led to the establishment of specific HbA1C targets for diabetes care with the goal of preventing or delaying the development of long-term complications. The major objective of diagnosing diabetes is to prevent premature mortality and complication-related morbidity. Therefore it seems logical to consider diagnosis in terms of risk of complications. American Diabetes Association (ADA)-organized international expert committee in 2010 recommended the adoption of the HbA1C assay for the diagnosis of diabetes at a cut point of 6.5% (8). This cut point was primarily derived from a review of studies that examined the association of HbA1C values with incident retinopathy. Retinopathy was chosen as the ultimate criterion because it is among the main complications of diabetes.

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World Health Organization (WHO) in 2011 officially recommended HbA1C testing for the diagnosis and monitoring of diabetes. They recommend that HbA1C can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement (9,10).

**Standardization of HbA1C levels**

Currently there are several methods available to measure glycated hemoglobin, and it is of utmost importance that these methods are standardized to report the same result for a single blood sample. The American Association for Clinical Chemistry (AACC) established a committee in 1993 to standardize GHB/HbA1C results so that clinical laboratory results are comparable to those reported by the DCCT and UKPDS, which established direct relationships between HbA1C concentrations and outcome risks in patients with diabetes. Three years later the National Glycohemoglobin Standardization Program (NGSP) was established to execute the protocol developed by the AACC committee (11,12). The ADA recommends that laboratories use only HbA1C assays that are certified by NGSP as traceable to the DCCT reference. These assays are listed on the NGSP website (http://www.ngsp.org) and are updated at least annually.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) in 1995 developed a true reference method for HbA1C which is known as IFCC standardization. The IFCC reference method is technically demanding, time consuming, and very expensive and is not designed for routine analysis of patient samples. IFCC measurement is too specific as it only measures one molecular species of HbA1C: thus, non-HbA1C components are not included in final results. Therefore it was found that HbA1C values obtained by using IFCC method are 1.5 to 2 percentage points lower than the NGSP results traced to DCCT (13). To overcome this problem a “master equation” was developed to formulize the relationship between the IFCC reference method and the NGSP. The master equation allows for the conversion of the IFCC results to more customary HbA1c results (14).

In 2007, the IFCC recommended that HbA1C results be expressed as mmol HbA1c/mol Hb instead of an HbA1C percentage. To eliminate confusion on reporting of HbA1C, ADA, IDF and IFCC jointly issued a consensus statement in May 2007 which states that, HbA1C results were to be reported worldwide in IFCC units (mmol glycated Hb /mol total Hb) and derived NGSP units (%), using the IFCCNGSP master equation (15).

<table>
<thead>
<tr>
<th>Table 1. The pros and cons of diagnosing diabetes with HbA1C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reasons to prefer HbA1C</strong></td>
</tr>
<tr>
<td>HbA1C captures chronic hyperglycemia but not FPG</td>
</tr>
<tr>
<td>Fasting not needed</td>
</tr>
<tr>
<td>Better associated with chronic complications than FPG</td>
</tr>
<tr>
<td>Microangiopathic complications (retinopathy) are associated with HbA1C as strongly as with FPG</td>
</tr>
<tr>
<td>No acute perturbations (e.g., stress, diet, exercise, smoking) affect HbA1C</td>
</tr>
<tr>
<td>Has a greater pre-analytical stability than blood glucose</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 2. Some of the factors that influence HbA1C and its measurement</th>
</tr>
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<tbody>
<tr>
<td><strong>Factors causing increased HbA1C</strong></td>
</tr>
<tr>
<td>Iron deficiency anemia (17), vitamin B12 deficiency</td>
</tr>
<tr>
<td>Alcoholism</td>
</tr>
<tr>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Splenectomy</td>
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<td></td>
</tr>
</tbody>
</table>
Correlation of HbA1C with average glucose

ADA and the American Association of Clinical Chemists (AACC) have published the correlation between HbA1C levels and mean plasma glucose levels based on data from the international A1C-Derived Average Glucose (ADAG) trial. ADAG trial utilizes frequent patient self-monitoring of blood glucose (SMBG) and continuous glucose monitoring (CGM) in 507 adults (83% Caucasian) with type 1, type 2, and no diabetes. Correlation of 0.92 is considered strong enough to justify reporting both an A1C result and an estimated average glucose result when a clinician orders the HbA1C test (19). For patients in whom HbA1C and measured blood glucose appear discrepant, the possibilities of hemoglobinopathy or altered red cell turnover should be considered (Table 2). Clinicians should also use the options of more frequent and different timing of SMBG or use of CGM. Other measures of chronic glycemia such as fructosamine are available, but their linkage to average glucose and their prognostic significance are not as clear as is the case for HbA1C (19,20). A calculator for converting HbA1C results into mean plasma glucose is available at http://professional.diabetes.org

<table>
<thead>
<tr>
<th>HbA1C (%)</th>
<th>Mean Plasma Glucose (mg/dl)</th>
<th>Mean Plasma Glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
<td>8.6</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
<td>10.2</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
<td>11.8</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
<td>13.4</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
<td>14.9</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
<td>16.5</td>
</tr>
</tbody>
</table>

HbA1C level and future risk of diabetes

Systematic review of various prospective studies confirms a strong, continuous association between HbA1C and subsequent diabetes risk. Persons with an HbA1C value of ≥6.0% have a very high risk of developing clinically defined diabetes in the near future with 5-year risks ranging from 25 to 50% and relative risks frequently 20 times higher compared with HbA1C <5%. However, persons with an HbA1C between 5.5 and 6.0% also have a substantially increased risk of diabetes with 5-year incidences ranging from 9 to 25%. The ideal decision about what HbA1C cut point is used for intervention should ultimately be based on the capacity for benefit as shown in clinical trials. Findings from various studies suggest that HbA1C range of 5.5 and 6.5% will capture a large portion of people at high risk, and if interventions can be employed to this target population, it may bring about significant absolute risk reduction (21,22). ADA recommends that patients with HbA1C of 5.7-6.4% should be referred for lifestyle modifications with or without metformin to prevent the development of diabetes in these patients (1).

Conclusion

HbA1C has achieved importance in diabetes because of its value in the evaluation of glucose control and its relation to long-term microvascular complications. The utility and convenience of HbA1C compared with plasma glucose for the diagnosis and management of diabetes has to be weighed against the fact that it is not readily available in many countries and the cost remains unaffordable to most of our patients. Inaccuracies in measurement and poor standardization of HbA1C assays are still a common problem, even in western countries. Therefore it should be used in the management of diabetes only if the assays are standardized to criteria aligned to the international reference values.

References


Rational use of oral antidiabetic drugs during War Dwin, the Buddhist Lent

Tint Swe Latt, Sanjay Kalra¹, Rakesh Sahay²


Abstract

The Buddhist Lent (known as War Dwin in Myanmar) is a 3 lunar month long period of fasting observed by devout Buddhist during the monsoon each summer. Dietary patterns during the War Dwin pose a challenge for patients with diabetes who wish to fast, as well as for diabetes care providers who have to provide effective, yet safe therapeutic regimes. During the War Dwin, people take solid meals only from midnight to noon. Intake is limited to jaggery and from noon to midnight. This predisposes to hypoglycemia, which in turn encourages defensive snacking and leads to poor glycemic control.

This article discusses rational oral drug therapeutic options during War Dwin.

It draws from available pharmacological evidence, combined with clinical experience, to suggest possible antidiabetic regimes which combine efficacy with safety and tolerability.

Key words: Alpha-glucosidase inhibitors, Buddhism, diabetes, dipeptidyl peptidase-4 inhibitors, gliclazide, glimepiride, metformin, pioglitazone, religion, type 2 diabetes.

Introduction

Buddhism is one of the major world religions, and has adherents in every continent of the world. It is the main religion of a large number of Asian countries, including Sri Lanka, Bhutan, Myanmar, Thailand, Laos, Cambodia, and Vietnam. These countries have not escaped the diabetes pandemic, and they report increasing prevalence of diabetes in recent years (1). The Buddhist Lent (known as War Dwin in Myanmar) is 3 lunar month long annual period of fasting observed by devout Buddhists during every monsoon. This poses a special health challenge for people with diabetes who wish to observe the fast, and follow a specific dietary restriction associated with it.

The Buddhist Lent fast is characterized by a 12-h long fasting period (in Myanmar) (noon to midnight) and a 12-h long period in which the fast is broken (midnight to noon). The long duration of the period (3 months) as well as the 12 hourly cycles of fasting and eating makes it a major challenge for the devout. This is especially true for the elderly, who are usually keener on fasting, and for those with diabetes, who face challenges related to glycemic control.

Extensive literature has been published, including from South Asia, on management of diabetes during Ramadan (2). It is surprising that only scanty references are available on the impact of Buddhist Lent on diabetes, and vice versa, in English literature.

As the prevalence of diabetes increase in Buddhist countries, and as the age of onset of diabetes falls, a greater number of devout Buddhist with diabetes will request their doctor for advice on how to fast in a healthy manner. Healthcare providers, however, are often not sensitized to the specific needs and requirement for this patient population.

This communication tries to address this issue. While it focuses on Myanmar tradition, it is equally relevant to other countries of the region. The proposed management strategies are written in a style that can be followed by all healthcare providers, including specialist diabetologists and diabetes nurses. This article also hopes to stimulate, in English language medical literature, a discussion, and an eventual consensus-building, on appropriate management of diabetes during the Buddhist Lent.

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Nutrition during the Buddhist Lent

The Buddhist Lent is characterized by strict and stringent rules regarding food intake. Each day of the 3-month long period is divided into two 12-h long periods; keeping the fast from noon to midnight and breaking it from midnight to noon.

During the fasting period, devout Buddhists can drink liquids, but are not allowed to take solids or alcohol. People tend to take high caloric liquids; including fruit juice, soya bean milk, and soft drinks; apart from green tea and water. Most people take jaggery and a few people accept ginger, onion, and fruits during the fast. During the rest of the day, people often take a small snack after midnight, a normal serving of breakfast, and heavy lunch before noon.

Lent is the time of meditation as well as fasting. People engaged in meditation at multiple times, both during fasting and feasting period. Meditation while sitting (ta yar myat) and while walking (ta yar theim) are allowed.

Impact of lent on diabetes

Diabetes is a multifaceted disease with varied complications. Patient with diabetes often have to juggle strict dietary advice, complex therapeutic regimes (both oral and injectable), and rigid lifestyle to manage their condition. It may become difficult for them to adjust their life style and dietary patterns to conform to religious guidance. Acute complications such as hypoglycemia caused by delayed meals and hyperglycemia because of defensive snacking and calorie rich food intake tend to occur more frequently during fasts. Chronic complications, both macrovascular and microvascular, may worsen during prolonged fasting, as a corollary of poor glycemic control. Hypoglycemia may manifest only as subtle symptoms like lack of concentration, inability to meditate, or difficulty in practicing meditation. This is a delicate issue for the devout and must be probed with care and sensitivity.

Nutritional management

Suggestions to optimize nutritional intake for people with diabetes during Buddhist Lent have been published recently (3). One should encourage intake of small frequent meals during the feasting period, while advising frequent intake of low or medium calorie liquids during the fast.

The nutritional and drug management of diabetes should be planned in accordance with each other. Drug therapy should be tailored according to the diet of the patient (4).

The patient dietary and exercise habits should be reviewed and modified. Low calorie drink such as lemonade, green tea, soya bean milk, and freshly squeezed fruit juice should be encouraged. Calorie rich drink like soft drinks and processed juice should be avoided.

Meals may be modified to reduce calorie content and glycemic index. For example, boiled noodles (khat swae pyote) can replace fried noodles (khat swae chow) and help improve glycemic control.

Lifestyle modification, for example, changing from sitting meditation to walking meditation, may be suggested to the patient, while respecting his or her religious beliefs. Short episodic exercise (30 min of walking meditation, for example) may be proposed as an alternative to prolonged sitting or walking.

Physical activity management

While one should encourage physical activity at all times, it may not be feasible to do so during fasting. One can advise patient to perform walking meditation (ta yar myat) instead of sitting meditation (ta yar theim) wherever possible. This will help improve general health, while increasing calorie utilization and avoiding hyperglycemia.

Oral antidiabetic drug (OAD) initiation during Buddhist Lent

In a clinical scenario where OADs need to be initiated in a recently diagnosed type 2 diabetes patient, metformin is the drug of choice.

Metformin is economical, widely available, effective, and free of major side effects including hypoglycemia. It is recommended by major international guidelines as well. During Buddhist Lent, the following regime is suggested for initiation of conventional metformin with breakfast and sustained-release metformin with lunch. This will cover the postprandial period after breakfast, and provide sustained coverage post lunch, without any risk of hypoglycemia. In case metformin is contraindicated, another OAD can be used. If the patient is symptomatic, and needs insulin initiation, it may be safer to seek exemption from fasting. However, modern insulin analogues are available which make it easier to maintain adequate glycemic control while observing the Buddhist Lent.

If metformin is not tolerated or contraindicated, one may initiate therapy with pioglitazone, a dipeptidyl peptidase 4 (DPP4)-inhibitor or an alpha-glucosidase inhibitor during Lent. The relative advantages and disadvantages of these drugs have been discussed in detail recently.

During Lent, once daily administration of drug is preferred by most devout. Fixed dose combination (FDC)
fulfills this need by providing two or more drugs in single tablets. During Lent, in patients with significant hyperglycemia, or a high baseline hemoglobin A1c (HbA1c), one may initiate therapy with an FDC of metformin+pioglitazone, or metformin+DPP4-inhibitor.

Insulin secretagogues may also be used during Lent for initiation of therapy, if metformin is not tolerated. It is preferable to use drugs with a lower risk of hypoglycemia, such as low dose glimepiride, glipizide, or repaglinide. Long acing sulfonylureas such as glibenclamide (glyburide) should be avoided.

Oral drug modification during Buddhist Lent

Another clinical scenario that often occurs is decompensation of glycemic control Buddhist Lent, in a patient who was previously well controlled on OADs. The patient may present with hypoglycemia, hyperglycemia, or both, and this will necessitate modification of therapy. Various options are available to manage this situation.

Dose escalation or reduction

Patient who experience suboptimal control during Lent while on oral sensitizer therapy should have their drug dosage optimized, till submaximal dose is reached. Thus, a patient on low dose metformin should have his or her dose increased up to 1.5-2.0 g, or on pioglitazone up to 30 mg daily. Patient with high glucose levels taking sulfonylurea monotherapy may be offered dose escalation with great caution. Dose reduction is an easy way of managing hypoglycemia, irrespective of class of drug.

Change of preparation

Some patient may benefit from changing a sustained release to immediate release preparation. For example, patients who cannot maintain smooth glycemic control during Lent while on modified release gliclazide may be shifted to immediate release gliclazide twice daily. Similar changes may be made with metformin if needed.

Drug switch

Suboptimal control may be managed by switching a drug during Lent. This switch may be intraclass (e.g., from one sulfonylurea to another) or interclass (e.g., from one sensitizer to another). Patient with a tendency towards hyperglycemia may be changed from less potent sulfonylurea to more effective, yet safe, drugs like glimepiride. Those experiencing hypoglycemia too, with twice daily regimes of glipizide or once daily glibenclamide, may respond better to once daily glimepiride.

The shorter acting repaglinide may also be tried in twice daily regimes (with breakfast and lunch).

Intensification or deintensification

Patient on oral therapy who experience poor control may be offered intensification of therapy, by adding a second (or third) class of drugs. Basic clinical guidelines, as updated recently, should be followed. The use of FDCs offers comfort, convenience, compliance, and better control to the patient (6). Use of FDCs with scored tablets helps in accurate dose titration during the course of treatment.

Deintensification may be required for patient with biochemical or symptomatic hypoglycemia. Frequent hypoglycemia episodes may occur in patients on dual or triple combination therapy.

Differences between OAD use during Lent and otherwise

While much of the recommendations mentioned in this paper are similar to those of current international guidelines, a few suggestions make this article unique.

This paper highlights the differential utility of various preparation of the same molecule, for example, immediate- and sustained-release metformin. It follows that the authors also recommended careful and rational use of the appropriate preparation, based on target for glycemic control (fasting vs postprandial vs both) and side effect profile. This aspect of diabetes pharmacotherapy has not been highlighted earlier, though the different pharmacokinetics of various preparations of OADs allows ample choice to the prescriber.

This paper also suggests and recommends intraclass drug switch of sulfonylureas during Buddhist Lent. Though this is not recommended during routine practice, the unique dietary pattern of Buddhist Lent makes it imperative for doctors to ensure that appropriate OADs (including sulfonylurea) are prescribed.

A short acting preparation with breakfast and at lunch or a single acting drug at breakfast should be preferred. Examples include glipizide or gliclazide (conventional) twice a day and glimepiride once a day. Glibenclamide should be avoided.
Conclusion

The Buddhist Lent fast is an important part of life for the devout Buddhist. The unique dietary pattern followed during this 3 lunar month long period poses special challenges for the patients with diabetes. Rational prescription and modification of OADs, as detailed in this paper, along with appropriate nutritional and lifestyle advice, can help the devout patient with diabetes complete the Buddhist Lent fast. This can be done with minimal or no impact on the individuals health.

Table. OAD modification during Buddhist Lent

<table>
<thead>
<tr>
<th>Patient’s status/intervention</th>
<th>Euglycemia</th>
<th>Significant hypoglycemia</th>
<th>Significant hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>Reinforce dietary advice</td>
<td>• Frequent meals</td>
<td>• Low calorie meals, e.g., boiled noodles to replace fried noodles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liquid food supplements</td>
<td>• Low calorie liquids</td>
</tr>
<tr>
<td>Meditation</td>
<td>Reinforce healthy habits</td>
<td>Sitting meditation</td>
<td>Walking meditation</td>
</tr>
<tr>
<td>Dose change</td>
<td>None</td>
<td>Reduction</td>
<td>Escalation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Increase SU dose with caution</td>
</tr>
<tr>
<td>Change in pharmaceutic</td>
<td>Shift from modified release (long acting) to short acting gliclazide</td>
<td>Shift to IR to control PPG, shift to SR to control FPG</td>
<td></td>
</tr>
<tr>
<td>preparation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug substitution</td>
<td>None</td>
<td>Shift to safer SU, e.g., glimepiride or short acting meglitinide, e.g., repaglinide</td>
<td></td>
</tr>
<tr>
<td>• Interclass</td>
<td></td>
<td>Shift to rapid acting drug to control PPG, shift to longer acting drug to control FPG</td>
<td></td>
</tr>
<tr>
<td>• Interclass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensification or deintensification</td>
<td>None</td>
<td>Discontinue the more potent drug, e.g., SU</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Add another class of drug, e.g., secretagogue to sensitizer</td>
<td></td>
</tr>
</tbody>
</table>

OAD = Oral antidiabetic drug, SU = sulfonylurea, IR = immediate release, SR = sustained release

Source of Support: Nil, Conflict of Interest: Nil

References

Letter to the Editor

Nirogi Paadha: a step forward for the Sri Lankan Diabetic

Sri Lanka Journal of Diabetes, Endocrinology and Metabolism 2013; 3: 112-113

To the Editor,

The increased risk of wounding coupled with poor healing and amputation that involves diabetic feet is well known (1). Based on recent epidemiologic surveys in Sri Lanka, we are dealing with approximately 1.5 to 2 million diabetics as of now (2). With an annual rate of 5%, we are likely to be dealing with approximately 100,000 foot ulcers in diabetics every year (3). The resultant amputations, impairment of quality of life and cost must be enormous, although not quantified in Sri Lanka. The current focus on improving life expectancy alone is not sufficient. It is time we also pay due attention to quality of life issues; thus a strong commitment toward amputation prevention in Sri Lanka. Diabetes is the main cause for non traumatic amputations and is also a contributor/ marker of premature death (4). Hence there is an urgent need to focus on diabetic limb salvage in Sri Lanka.

The primary challenge in diabetic limb salvage involves prevention of wounding in the first place and when that fails, healing without progressing to amputation; thereby preserving independent ambulation and quality of life. But is this possible and if so how?

The Nirogi Paadha project of the Diabetes Prevention Task Force of the Sri Lanka Medical Association together with Sri Lankan League for the Prevention of Diabetic Foot Amputation and Endocrine Society of Sri Lanka have taken on this challenge. They need the support of all sectors of our health care system in order to succeed.

Success demands an understanding of what is going on with answers to the questions: “how” and “why”.

The key areas we need to recognize are:
1. Medical knowledge and skills
2. Implementation
3. Patient compliance issues and
4. The need to audit

No one doubts the need for knowledge and skills. Transfer of knowledge to medical officers and other members of the healthcare team on diabetic angiopathy, neuropathy and immunopathy with the complex interactions between these mechanistic factors is ongoing and must be sustained. But this alone is not sufficient. Non application of this knowledge into clinical practice makes the understanding worthless. In the words of J. A. Lindsay, “for one mistake made for not knowing, ten mistakes are made for not looking”. The problem does not end here. Having acquired the knowledge and applied it, the next stumbling block is non compliance by the patient. Adherence to the recommended diet, medication and physical activity program to achieve and maintain optimum glycaemic status, reduce other metabolic risks, and the avoidance of tobacco is a constant challenge. Poor compliance with use of appropriate footwear, daily foot inspection, immediate reporting of a fresh change and regular follow up of high risk feet is a global issue (5). We therefore need to evolve a home-grown system to overcome these problems amidst our resource limited structure. Finally we need to appreciate the necessity to audit. Data on the process and outcomes are essential to justify and direct any program, and this is no exception.

The initiative on ‘quality and safety’ in the Ministry of Health will have the opportunity to contribute in this respect.

What actually needs to be done? Patient education, assessment with risk categorization, provision of footwear, removal of callus, management of infection, ensuring healing and moreover maintenance of the healed state is the list in a nutshell. Nirogi Paadha project has developed the care plan covering all of the above in order to standardize and optimize the diabetic foot service in Sri Lanka. What is striking here is that no one person can deliver such a wide array of services to a patient. Many people will have to work together in a coordinated fashion towards the common goal of amputation prevention – Nirogi Paadha. A limb salvage team in Sri Lanka! After all, we have the necessary members in all our hospitals, i.e. medical, surgical, nursing and others, but no teams. The Nirogi program is attempting to focus on these issues and attempts to introduce a team concept at hospital level and later bring in community healthcare workers to further enhance compliance, reduce complications and cost and most importantly reduce the workload on hospitals.

Finally we need to be able to offer appropriate footwear to protect insensate feet and it is noteworthy that the project has collaborated with DSI group of companies to provide general footwear at an affordable price throughout the country. This is in parallel with arrangements for training of Orthotists to provide for specialized custom-made footwear in collaboration with the Sri Lankan Society of Prosthetics and Orthotics based at the Ragama Rehabilitation Hospital.
We must remember that success is not the destination but a journey and what matters most is where we are and the direction in which we are moving. In our attempts to salvage the diabetic foot, the destination is clear, the path is known and the journey has just begun. But the road ahead is full of obstacles and needs the support of all in order to reach the destination, Nirogi Paadha.

Your attention is drawn to the Practice Guidelines developed by all stakeholders and officially launched in July 2013.

References

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**Sodium Disorders: Hyponatraemia**

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**Introduction**

Hyponatraemia is the most common electrolyte abnormality observed in hospitalized patients, and is associated with complications such as seizures, increased mortality and prolonged hospitalization. The risk of symptoms, complications and death increases with severity of hyponatraemia (1).

**Table 1. Levels of severity of hyponatraemia**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Serum sodium (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>130-134</td>
</tr>
<tr>
<td>Moderate</td>
<td>120-129</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;120</td>
</tr>
</tbody>
</table>

**Table 2. Symptoms of hyponatraemia**

The symptoms of hyponatraemia are primarily neurological, and worsen as sodium concentration drops (4). They include:

- Headache
- Nausea, loss of appetite, vomiting
- Malaise
- Lethargy
- Weakness
- Poor coordination
- Muscle cramps
- Somnolence
- Disorientation
- Personality change

**Table 3. Complications of severe and rapidly evolving hyponatraemia** (5)

- Seizures
- Coma
- Permanent brain damage
- Respiratory arrest
- Brain-stem herniation
- Death

**Epidemiology**

- Hyponatraemia occurs in 15% of hospitalized patients. 67% of cases are hospital acquired (6,7).

**Evaluation of hyponatraemia**

The Aims of evaluation are:

- To identify possible cause(s) and
- To decide the best treatment

This is achieved through clinical evaluation and relevant laboratory investigations.

Disclaimers:

Clinical Practice Guidelines are developed to be of assistance to health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient’s individual circumstances.

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Clinical evaluation

- Assess the Severity: Conscious level and mental Status
- Assess the duration of hyponatraemia
- Assess Volume Status: (hypovolaemic/euvolaemic/hypervolaemic)
  - Look at mucous membranes, skin turgor, dependent edema, JVP, pulse, blood pressure, postural drop
  - Check urine colour/concentration and volume
  - Go through fluid balance chart (polyuria, negative vs. positive fluid balance)
  - Assess Central Venous Pressure if feasible
- Go through the drug history carefully: identify any causative drugs such as diuretics, ACEI/ARB, NSAIDs, anti-epileptics, chemotherapeutic agents etc.
- Look for underlying illness: Congestive cardiac failure, cirrhosis, renal failure, nephrotic syndrome, hypothyroidism
- Look for possible etiology: SIADH, CSW (Cerebral salt wasting), SAH (Sub arachnoid hemorrhage)

Laboratory Investigations

- Urine Spot Sodium with simultaneous Serum Sodium
- Urine Osmolality and Serum Osmolality (optional)

Patients may require other tests to exclude possible underlying aetiology of hyponatraemia depending on clinical suspicion.
E.g. Primary polydipsia, Hypothyroidism, Hypoadrenalism

Sodium Disorders: Hyponatraemia
Management of hyponatraemia

General Rules

1. The presence or absence of symptoms and the duration of the hyponatraemia should guide the treatment strategy.
2. Extra caution should be taken in managing neurosurgical hyponatraemia as symptoms may be more prominent in patients with cerebral insults but may not reflect the hyponatraemia per se.
3. If an underlying cause can be identified, specific therapy is indicated.

E.g.: • Stopping diuretics
• Instituting appropriate hormone replacement therapy for glucocorticoid insufficiency and/or hypothyroidism

Main Principles

• Avoid overcorrection
• In chronic hyponatraemia serum sodium must be monitored closely and corrected no faster than
  o 10-12 mmol/L in the first 24 hours
  o 18 mmol/L in the first 48 hours
• In the presence of predisposing factors for central pontine myelinolysis correction rate should be even lower (≤ 8 mmol/L in 24 h period).
• Acute hyponatraemia (duration < 48 h) can be safely corrected more quickly than chronic hyponatraemia.
• In severe symptomatic patients (e.g., severe confusion, coma, seizures), hypertonic saline is indicated with the therapeutic target being improvement of symptoms or serum sodium > 120 mmol/L.

Central pontine myelinolysis (osmotic demyelination syndrome)

Characterized by focal demyelination in the pons and extrapontine areas causing serious neurologic sequelae (10).

Risk factors for central pontine myelinolysis in the hyponatraemic patient are:
• Serum sodium of less than 120 mmol/L for more than 48 hours
• Aggressive IV fluid therapy with hypertonic saline solutions
• Development of hyponatraemia during treatment (overcorrection)
• Hypokalaemia
• Alcoholism and/or malnutrition
• Liver disease

SIADH

• Diagnostic Criteria (9)
  o Serum osmolality <275 mOsm/kg with inappropriately high urinary osmolality >100 mOsm/kg
  o Clinical euvolaemia
  o Elevated urinary sodium excretion (Urine Spot Sodium > 40 mmol/L) with normal salt and water intake
  o Absence of other causes of euvolaemic hyposmolality
• Once SIADH is diagnosed it is recommended to look for possible underlying aetiology e.g. drugs (anti-epileptics, anti-psychotics etc.), CNS and lung pathology, malignancy

Management of hyponatraemia in SIADH

• Cornerstone of SIADH treatment is fluid restriction
• Severe symptomatic SIADH can be treated with hypertonic saline
• SIADH may be treated with urea, diuretics, lithium, demeclocycline, vaptans and/or fluid restriction

Management of hyponatraemia in SAH (8)

• Hyponatraemia in SAH patients at risk of vasospasm should not be treated with fluid restriction
• Patients with severe symptoms or subarachnoid haemorrhage (SAH) at risk of vasospasm should receive hypertonic saline
• SAH patients should receive treatment even for a serum sodium level of 131 to 135 mmol/L.
• Sodium should not be corrected by more than 10 mmol/d
• Fludrocortisone may be considered in the treatment of hyponatraemia in SAH patients at risk of vasospasm
• Hydrocortisone may be used to prevent natriuresis in SAH patients
• CSW should be treated with replacement of sodium and intravenous fluids
Sodium Disorders: Hyponatraemia

Hypertonic saline correction

- Multiply weight by desired correction rate and infuse as ml/h of 3% saline.
- Target rate of correction is 1.5 to 2 mmol/L per hour with 3% saline for the first 3 to 4 hours, or more briefly, if symptoms improve or the sodium level exceeds 120 mmol/L.

E.g. in a 70 kg patient in whom the desired correction rate is 0.5 mmol/hour, the rate of infusion would be (70 × 0.5) 35 ml/hour.
Principles of fluid restriction

General guidelines:
- Restrict all intake that is consumed by drinking, not just water
- Aim for a fluid restriction that is 500 ml/d below the 24-hour urine output
- Do not restrict sodium unless indicated

Predictors of failure of fluid restriction:
- Urine sodium + potassium is greater than the serum sodium
- 24-hour urine output is less than 1,500 ml
- Increase in serum sodium after fluid restriction is less than 2 mmol/L in 24h
- High urine osmolality (>500 mOsm/kg H2O)

How much to restrict / How much to give?

\[ \text{U/P ratio} = \frac{U_{Na} + U_{K}}{P_{Na}} \]

\(U_{Na}\) is the urinary \([Na^+]\), UK is the urinary \([K^+]\) and \(P_{Na}\) is the plasma/serum \([Na^+]\). This simplified equation can be used to estimate free water loss in relation to the effective osmoles within the blood plasma (11).

Table 4. Recommended fluid consumption based on patient’s U/P sodium ratio

<table>
<thead>
<tr>
<th>Urine/plasma Na⁺ ratio</th>
<th>Insensible water losses</th>
<th>Expected net water loss</th>
<th>Recommended fluid consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.0</td>
<td>800 ml</td>
<td>800 ml</td>
<td>No oral fluids, use IV fluids if indicated</td>
</tr>
<tr>
<td>1.0 - 0.5</td>
<td>800 ml</td>
<td>800-1300 ml</td>
<td>Up to 500 ml</td>
</tr>
<tr>
<td>≤ 0.5</td>
<td>800 ml</td>
<td>1300-1500 ml</td>
<td>Up to 1000 ml</td>
</tr>
</tbody>
</table>

References
Sodium Disorders: Hypernatraemia

Introduction

Hypernatraemia is defined as serum sodium concentration above 145 mmol/L. Hypernatraemia invariably denotes hypertonic hyperosmolality and always leads to cellular dehydration.

Epidemiology

Hypernatraemia occurs in approximately 1% of hospitalized patients and incidence increases in debilitated elderly persons and in breastfed infants. Hypernatremia is associated with high morbidity and mortality and mortality rates are as high as 50% (5).

Etiology

The causes of hypernatraemia are listed in table 1 however there may be more than one factor operational particularly in critically ill patients.

<table>
<thead>
<tr>
<th>Table 1. Causes of hypernatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pure water deficit</td>
</tr>
<tr>
<td>• Inadequate intake or excessive insensible loss</td>
</tr>
<tr>
<td>• Renal loss</td>
</tr>
<tr>
<td>o Diabetes insipidus (central or nephrogenic)</td>
</tr>
<tr>
<td>2. Water and sodium deficit</td>
</tr>
<tr>
<td>• Extra renal loss</td>
</tr>
<tr>
<td>o Skin (burns, excessive sweating)</td>
</tr>
<tr>
<td>o Gastrointestinal Tract (viral gastroenteritis, osmotic diarrhea, vomiting)</td>
</tr>
<tr>
<td>• Renal loss</td>
</tr>
<tr>
<td>o Osmotic diuresis (hyperglycaemia, mannitol, high protein diet)</td>
</tr>
<tr>
<td>o Renal disease</td>
</tr>
<tr>
<td>o Post obstructive diuresis</td>
</tr>
<tr>
<td>o Resolving or polyuric phase of acute tubular necrosis</td>
</tr>
<tr>
<td>3. Sodium gain</td>
</tr>
<tr>
<td>• Hypertonic saline infusion</td>
</tr>
<tr>
<td>• Hypertonic feeding</td>
</tr>
<tr>
<td>4. Transient</td>
</tr>
<tr>
<td>• After seizure or vigorous activity</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Table 2. Clinical features of hypernatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features in adults</td>
</tr>
<tr>
<td>• Anorexia/nausea/vomiting</td>
</tr>
<tr>
<td>• Restlessness</td>
</tr>
<tr>
<td>• Twitching</td>
</tr>
<tr>
<td>• Hyperreflexia</td>
</tr>
<tr>
<td>• Ataxia</td>
</tr>
<tr>
<td>• Tremor</td>
</tr>
<tr>
<td>• Lethargy/irritability/stupor/coma</td>
</tr>
<tr>
<td>Clinical features in children</td>
</tr>
<tr>
<td>• Hyperpnoea</td>
</tr>
<tr>
<td>• Muscle weakness</td>
</tr>
<tr>
<td>• Restlessness</td>
</tr>
<tr>
<td>• Characteristic high-pitched cry</td>
</tr>
<tr>
<td>• Insomnia</td>
</tr>
<tr>
<td>• Lethargy</td>
</tr>
<tr>
<td>• Coma</td>
</tr>
</tbody>
</table>

Adult patients generally have few symptoms until the serum sodium concentration exceeds 160 mmol/L. The level of consciousness is correlated with the severity of the hypernatremia. Brain shrinkage induced by hypernatremia can result in vascular rupture, with cerebral bleeding, subarachnoid hemorrhage and permanent neurologic damage or death.

Evaluation of hypernatraemia

History

• Obvious water loss with no adequate replacement of water. e.g. Diarrhoea, vomiting, altered mental status
• Symptoms and possible causes of diabetes insipidus (DI). e.g. polyuria, polydipsia, cerebral pathology, drug history (lithium)
• Urine output: increased or decreased
Management of hypernatraemia

Treatment of hypernatraemia requires a two pronged approach

- Correcting the prevailing hypertonicity.
- Addressing the underlying cause.

Correcting the prevailing hypertonicity

- The aim: Fall in the serum sodium concentration of 10 mmol/l per day (Except those in whom the disorder has developed over a period of hours).
- The goal: Reduce the serum sodium concentration to 145 mmol/l.
- The route: The preferred route for administering fluids is the oral route or a feeding tube; if neither is feasible, fluids should be given intravenously.
  - Type of fluid:
  - The more hypotonic the infusate, the lower the infusion rate required.
  - Except in cases of frank circulatory compromise, 0.9% saline is unsuitable for managing hypernatraemia.
  - Rate of infusion:

  \[
  \text{Change in serum } \text{Na}^+ \text{ per litre of infusate} = \frac{(\text{infusate } \text{Na}^+) - (\text{serum } \text{Na}^+)}{\text{(total body water) + 1}}
  \]

  Usually total body water is calculated as 0.5 × lean body weight

Table 3. Amount of sodium in various types of IV fluids

<table>
<thead>
<tr>
<th>Infusate</th>
<th>Na⁺ (mmol per litre)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% dextrose in water</td>
<td>0</td>
</tr>
<tr>
<td>0.2% NaCl in 5% dextrose</td>
<td>34</td>
</tr>
<tr>
<td>0.45% sodium chloride</td>
<td>77</td>
</tr>
<tr>
<td>Ringer’s lactate</td>
<td>130</td>
</tr>
<tr>
<td>0.9% sodium chloride</td>
<td>154</td>
</tr>
</tbody>
</table>

E.g. If 5% dextrose is selected as the infusate to correct a sodium of 160 mmol/l in a 60kg young male:

- Change in serum Na⁺ per litre of infusate:
  \[
  = \frac{0 - (160)}{(60 \times 0.5) + 1} = -5.2
  \]

- The aim is to reduce the sodium by 10 mmol/l per day

- Therefore the amount of 5% dextrose required per day = 10/5.2 = 1.9 litre per day or 80 ml/hour

Managing the underlying cause

- Stopping the gastrointestinal fluid losses
- Treating the pyrexia
- Correcting the hyperglycaemia
- Treating hypercalcaemia and hypokalaemia
- Withholding lactulose and lithium
- Correcting the feeding preparation
- Apart from these causes patients with cranial or nephrogenic diabetes insipidus has to be managed with adequate ADH or ADH- analogs.
**Cranial diabetes insipidus**

The treatment of choice for those with significant symptoms,

- DDAVP – (synthetic, long-acting vasopressin analogue): intranasal spray (10-40 mcg daily), parenteral injection (0.1-1.0 mcg daily) or oral (100-1000 mcg daily), in divided doses.
- There is wide individual variation in the dose required to control symptoms.
- Dilutional hyponatraemia is the most serious potential adverse effect.

**Nephrogenic diabetes insipidus**

- Secondary/acquired cases are managed by removing the underlying cause.
- Ensure adequate hydration.
- There are various treatment options including:
  - High dose DDAVP: may produce a response in partial nephrogenic diabetes insipidus, especially if the lesion is acquired.
  - Diuretics
    - Amiloride is beneficial in patients with reversible lithium nephrotoxicity.
    - Thiazide diuretics: hydrochlorothiazide 25 mg/day.
  - Non-steroidal anti-inflammatory drugs:
    - Ibuprofen 200 mg/day. (caution in renal impairment)
  - Low salt diets.

**References**

Annexure 1

Water deprivation test

Indications for water deprivation test

• Suspected cranial/nephrogenic DI
• To rule out primary polydipsia

Water deprivation test

• Patient voids at the beginning of test and starting weight is recorded
• Nothing allowed by mouth
• Sample is taken for serum Na
• Each voided urine is measured and corresponding urine osmolality is measured
• Weigh the patient hourly and document
• When patient has lost 3% of body weight/ 2 consecutive urine osmolality differ no more than 10% blood for serum Na and osmolality is drawn.

• Patient is given 2μg of desmopressin iv/im
• Urine output and osmolality measured hourly for another 2 hours

Interpretation

• In normal individuals, when plasma osmolality rises [>295 mosm/kg] vasopressin [ADH] secretion is stimulated and urinary concentration is increased; usually > 600mosm/kg. There is no further rise in urine osmolality when exogenous ADH is given as endogenous ADH effect is maximum.
• Cranial DI – rise in urine osmolality > 50% after desmopressin
• Nephrogenic DI – rise in urine osmolality < 10%
• Intermediate values in partial cranial/nephrogenic DI, osmotic diuresis

Table. Interpretation of urine osmolality [mosm/kg]

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>After fluid deprivation</th>
<th>After desmopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial DI</td>
<td>&lt;300</td>
<td>&gt;800</td>
</tr>
<tr>
<td>Nephrogenic DI</td>
<td>&lt;300</td>
<td>&lt;300</td>
</tr>
<tr>
<td>Primary polydipsia</td>
<td>&gt;800</td>
<td>&gt;800</td>
</tr>
<tr>
<td>Partial DI/polydipsia</td>
<td>300-800</td>
<td>&lt;800</td>
</tr>
</tbody>
</table>
The use of Inferior Petrosal Sinus Sampling (IPSS) without CRH stimulation in the Diagnostic Evaluation of ACTH dependent Cushing Syndrome (CS): Sri Lankan Experience

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Background

Differentiation between Cushing disease (CD) and ectopic ACTH syndrome (EAS) is challenging due to overlapping biochemical features and poor sensitivity of pituitary MRI in the detection of CD. IPSS with CRH stimulation is the gold standard method to evaluate ACTH dependent CS. In centres with suitable expertise, it has a sensitivity of 97% and specificity of 100% for diagnosing CD (1). However, CRH is expensive and therefore it is not used in South Asian region.

Objective

To assess the efficacy of IPSS without CRH stimulation in the evaluation of ACTH dependent CS.

Methods

This study was a retrospective analytical study conducted at the National Hospital of Sri Lanka. IPSS (with measurement of basal state ACTH gradient) was performed in ten patients with biochemically proven ACTH dependent CS. These patients had either normal pituitary or pituitary microadenoma less than 6 mm in size. The efficacy of IPSS was assessed by comparing catheter study results with histopathological diagnosis which included nine cases of CD and one case of EAS. A basal state Inferior petrosal sinus: Peripheral vein (IPS:PV) ACTH gradient of at least 2 was considered diagnostic of CD.

Results

The results of IPSS are shown in Table 1. A basal state IPS:PV ACTH gradient of at least 2 was observed in eight out of nine patients with histologically proven CD (sensitivity 88.8%). Average basal state ACTH gradient was 6.43 (range 1.20 - 19.53). IPSS without CRH stimulation could correctly exclude pituitary source of ACTH secretion in the patient with EAS (Basal IPS: PV ACTH gradient <2). Neurological complications were not observed during or after the procedure.

Figure 1. Anatomy of the venous drainage of the pituitary gland (2).
Abstracts of Free Papers

Table 1. IPSS Results

<table>
<thead>
<tr>
<th>Case</th>
<th>Histological Diagnosis</th>
<th>ACTH (pg/ml)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IPS (Dominant side)</td>
<td>Peripheral Vein</td>
<td>IPS/PV Gradient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CD</td>
<td>1680</td>
<td>86</td>
<td>19.53</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CD</td>
<td>1550</td>
<td>122</td>
<td>12.70</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CD</td>
<td>657</td>
<td>81</td>
<td>8.11</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CD</td>
<td>436</td>
<td>84</td>
<td>5.19</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CD</td>
<td>237</td>
<td>48</td>
<td>4.94</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CD</td>
<td>32</td>
<td>15</td>
<td>2.13</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CD</td>
<td>44</td>
<td>21</td>
<td>2.10</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CD</td>
<td>92</td>
<td>45</td>
<td>2.04</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>EAS</td>
<td>50</td>
<td>45</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CD</td>
<td>89</td>
<td>74</td>
<td>1.20</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion

In places where CRH is not available, IPSS with measurement of basal ACTH gradient appears to be effective in differentiating CD from EAS.

References


Background

Many clinical and biochemical critera are used to assess hyperandrogenism in subjects with Polycystic Ovary Syndrome (PCOS).

Objectives

To evaluate effectiveness of Modified Ferriman-Gallwey score (FG Score- hirsutism), serum total testosterone, and free androgen index (FAI), in the assessment of hyperandrogenism.

Methods

A case control study was conducted on 100 women aged 20-45 years (mean age=30). Confirmed cases with PCOS were age matched for controls from healthy volunteers. Recommended cut-offs used; FG >8, testosterone (T)>3.5 nmol/L, and free androgen index (FAI) >5. (Specific cutoffs for South Asians not been defined). Receiver operating characteristics (ROC) curves were drawn to compare diagnostic power of each parametre.

Results

N= 50 cases, 50 controls. Cases versus. Controls had significantly greater FG score, testosterone and FAI: median FG=10 versus. 3 (p= 0.00), mean T 2.76±1.78 versus.1.04±0.40(p= 0.00), mean FAI 7.31±7.55 versus.3.64±4.87 (p= 0.01); 76% cases and 4% controls had FG score> 8, 8.30% cases had elevated T with none among controls, 43.3% cases and 14.7% controls had FAI>5. The diagnostic power of T was greater than that of FAI in subjects with FG score>8. In ROC curve, area under the curve (AUC) for T and FAI were 0.832 and 0.766 respectively. T had 27% sensitivity and 97.5% specificity at cut-off 3.5 and FAI had 50% sensitivity and 87.5% specificity at cut-off of 5, in Sri Lankan PCOS subjects.

Modified Ferriman-Gallwey score, Serum Testosterone level and Free Androgen Index, in assessment of Hyperandrogenism in subjects with Polycystic Ovary Syndrome

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Sri Lanka Journal of Diabetes, Endocrinology and Metabolism
Conclusions
The clinical assessment by FG score detects hyperandrogenism in PCOS subjects more frequently compared to biochemical tests, testosterone and FAI. A higher detection rate was observed in controls when FAI was used as the indicator, suggesting a possible influence from changes in SHBG concentration. Total testosterone had greater diagnostic power than FAI.

Prevalence and types of lipid abnormalities in patients with newly diagnosed type 2 diabetes mellitus: A clinic based prospective study

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2 National Hospital of Sri Lanka, Colombo.

Objective
The objective of this study was to determine the prevalence and types of lipid abnormalities in patients with newly diagnosed type 2 diabetes mellitus in Sri Lanka.

Method
370 consecutive newly diagnosed patients with type 2 diabetes mellitus above 18 years referred to diabetes clinic at Teaching Hospital, Peradeniya from 1st of October 2009 to 30th September 2010 were enrolled. Height, weight, blood pressure, overnight fasting lipid profile and HbA1c were determined in all patients at first clinic visit.

Results
There were 234 (63.2%) females and 136 (36.8%) males. The mean age (±SD) of the population was 50.1±11.7 yrs. The commonest lipid abnormality was hypercholesterolemia, observed in 61.5% of the patients followed by high LDL observed in 51% of the patients. 39.5% of the patients had hypertriglyceridaemia while 26% patients had low HDL. Overall prevalence of any of these lipid abnormalities was 84%. Although prevalence of low HDL was significantly higher in females than males (51.7% vs. 16.1%; P<0.001), there were no differences in prevalence of hypercholesterolaemia, high LDL and hypertriglyceridaemia in females and males. The prevalence of hypercholesterolaemia, high LDL, hypertriglyceridaemia and low HDL was significantly associated with central obesity. There was no significant correlation between the fasting lipid levels with patient’s age, BMI, blood pressure and HbA1c levels. The mean for total cholesterol was 213.2±49.6, for triglyceride 148.0±67.5, for LDL 136.3±46.4, and for HDL 48.6±7.9 mg/dl.

Conclusion
Even at the time of diagnosis, the prevalence of lipid abnormalities is very high in our diabetes population. The commonest lipid abnormalities observed in this population are low HDL level followed by hypercholesterolaemia.

Acromegaly: Outcome of management at National Hospital of Sri Lanka

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Introduction
Many of the treatment modalities recommended for acromegaly are either too expensive or not available in Sri Lanka. There is a dearth of treatment and outcome data in Sri Lankan patients.

Objectives
The purpose of this study was to describe the demographic factors, presentation and comorbidities in acromegaly patients, and to analyze the treatment modalities used and the respective outcomes which include remission, recurrence and mortality among patients with acromegaly.

Methods
This was a descriptive cross sectional study conducted among 72 acromegaly patients attending endocrinology clinic and pituitary clinic at National Hospital of Sri Lanka between January 2012 and June 2013. Pituitary adenomas were classified based on Hardy’s classifications. A remission criteria of nadir growth hormone level <1 mU/L after oral glucose tolerance test (OGTT) or less than 5 mU/L in a five point GH Day curve was used.

Results
54.1% were females. The mean age of the patients at the time of presentation was 39.52 (SD ± 12.8) years and the
mean duration of symptoms on presentation was 3.28 years (SD ± 2.7). The commonest presentations were changes in facial appearance and increase in shoe and ring sizes (88%). 81.8% had tumour grade II and above. 14.2% had prolactin cosecreting with GH. 86.1% underwent TSS. 37.5% of patients with grade I tumour and 33.3% of patients with grade II tumour achieved remission following TSS. None of the patients with tumour grade III or above achieved remission following TSS. EBRT was effective in 20% in achieving remission. Medical therapy (either cabergoline or bromocriptine) as bridging/primary therapy achieved remission in only 20.8%. Irrespective of the mode of treatment no recurrence was noted in the patients who achieved remission. The mortality in this case series was 2.7%.

Conclusions
TSS remains the treatment of choice in acromegaly, though in grade III and IV tumours the success was limited. As most of the recommended options are very costly or unavailable in Sri Lanka, alternative treatment options generally used are EBRT or medical therapy (cabergoline/bromocriptine) which have limited efficacy.

Adrenal carcinoma with synchronous liver metastasis: A rare cause for Cushing’s syndrome
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Introduction
Adrenal carcinomas are uncommon. The incidence is approximately 0.6-1.67 cases per million persons per year. Females are more likely to get functional carcinomas. In the literature some reports suggest an increased predilection for the left adrenal. Approximately 60% of adrenal carcinomas will be functional with typical Cushiloid symptoms. Females will have features of androgen excess in addition. Most common sites for metastases are the lungs, liver, bone, and lymph nodes. The overall 5-year survival rate is approximately 20-35%.

Case report
Thirty four year old previously healthy female presented with clinical features of Cushing’s syndrome and androgen excess with ankle oedema, which is atypical for the clinical picture. She was found to have hypertension with hypokalaemic alkalosis and diabetes on admission. She had hepatomegaly, L/S retroperitoneal mass, mild ascites and bilateral ankle oedema. On investigations, she had biochemical evidence of ACTH independent Cushing’s syndrome and androgen excess. Mineralocorticoid axis was not investigated in detail. She was found to have L/S adrenal carcinoma with liver metastasis in USS abdomen and CT abdomen.

She was started on ketoconazole and debulking surgery was planned followed by chemotherapy. But while awaiting surgery she developed acute liver failure and died within 2 weeks from diagnosis.

Conclusion
Metastatic adrenal carcinoma is a very rare cause of Cushing’s syndrome. It is an extremely virulent malignancy leading to severe morbidity and poor survival. We are left with very few treatment options for palliation. Early suspicion and recognition of disease would direct the patient for early surgery to achieve maximum survival benefit.

Association between Body Mass Index, Waist Hip Ratio, Impaired glucose tolerance and Acanthosis nigricans in Sri Lankan subjects with PCOS
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Introduction
Though Acanthosis nigricans (AN) is not a clinical criterion in diagnosis of Polycystic Ovary Syndrome (PCOS), it is considered an indicator of higher metabolic risk in South Asian women.

Objectives
Our aim was to find the association between Body Mass Index (BMI), Waist Hip Ratio (WHR), impaired glucose tolerance (IGT) and Acanthosis Nigricans in Sri Lankan subjects with PCOS.

Methods
Retrospective data analysis of 157 consecutive South Asian women diagnosed with PCOS in a specialized...
endocrine clinic in Colombo. After a detailed history and physical examination, anthropometric measurements were taken and a 75 g Oral Glucose Tolerance Test (OGTT) was performed. Subjects were categorized into two groups depending on the presence or absence of AN.

**Results**

The mean age, BMI, and WHR of the total study population were 25.2 years, 26.24 kg/m², and 0.88 respectively. Type 2 diabetes mellitus was found in 5.1% and 17.8% had IGT. Of these 157 subjects, 104 (66.24%) had AN.

BMI > 23 Kg/m² was found in 84.6% subjects with AN and 41.5% subjects without AN. Mean BMI of the AN present and absent groups were 27.7 kg/m² and 23.3 kg/m² respectively. Mean WHR were 0.896 and 0.849 in AN present and absent groups. 65.4% of patients with AN and 52.8% patients without AN had a WHR above the cutoff value. In subjects with AN, following the 75 g OGTT 6.8% were diagnosed to have type 2 diabetes mellitus and 22.1% had IGT. In the group without AN these percentages were 1.9% and 9.4% respectively. The subjects with AN had significantly higher BMI, WHR and abnormal glucose tolerance (AGT) compared to those without AN. AN, by logistic regression analysis, was found to be an independent predictor for A GT, with an odds ratio of 3.176 (95% confidence interval= 1.229-8.209).

**Conclusion and recommendations**

Presence of AN suggests a severe end of the spectrum of PCOS with higher BMI, WHR and higher risk of A GT in South Asians. AN is an independent predictor of A GT. It is therefore recommended to use this clinical indicator in the risk assessment of subjects with PCOS in south Asia.

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**The use of Internal Jugular venous sampling (IJVS) as an alternative to Inferior Petrosal Sinus Sampling (IPSS) in the Diagnostic Evaluation of ACTH dependent Cushing Syndrome (CS): Sri Lankan Experience**

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**Background**

IPSS is the gold standard method to evaluate ACTH dependent CS. However, IPSS is not widely available, because it is technically demanding and requires an experienced interventional radiologist. In contrast, IJVS is technically easier and may be safer, because the catheters are not advanced as far. Therefore, IJVS may become an alternative to IPSS in centers without suitable expertise, if this investigation has good sensitivity and specificity to detect Cushing disease (CD). One study which included 65 patients demonstrated that IJVS with CRH stimulation had a sensitivity of 83% for diagnosing CD (1). However, no data available on the efficacy of IJVS without CRH stimulation in the evaluation of ACTH dependent CS.

**Objective**

To compare the efficacy of IJVS with IPSS in the evaluation of ACTH dependent CS.

**Methods**

This study was a retrospective analytical study conducted at the National Hospital of Sri Lanka. Both IPSS and IJVS (with measurement of basal state ACTH gradient) were performed sequentially in ten patients with biochemically proven ACTH dependent CS. These patients had either normal pituitary or pituitary microadenoma less than 6 mm
in size. The efficacy of IJVS and IPSS were assessed by comparing catheter study results with histopathological diagnosis which included nine cases of CD and one case of EAS. A basal state central (either IPS or IJV) to peripheral vein (PV) ACTH gradient of at least 2 was considered diagnostic of CD.

Results
The catheter study results were shown in Table 1. Out of nine patients with histologically proven CD, IJVS and IPSS correctly identified CD in seven and eight cases respectively. In this study, IJVS has slightly lower sensitivity (77.7%) in the localization of CD when compared with IPSS (88.8%).

Also, the average IJS/PV ACTH gradient (3.6) was lower when compared with that of IPS/PV (6.43). The dilution of blood in IJV due to drainage of other veins may be the explanation for this finding.

Both IPSS and IJVS could correctly exclude pituitary source of excess ACTH secretion in the patient with EAS (specificity 100%).

Conclusion
Centers without suitable expertise may choose to use the simpler IJVS and refer patients for IPSS when the results are negative. However, further large scale studies are necessary to assess the efficacy of IJVS without CRH stimulation in the evaluation of ACTH dependent CS.

References
medical clinics and general practitioners (GPs), were recruited for the study. Data were collected using an interviewer administered questionnaire.

Results
Out of 247 patients, 201 (81.3%) patients attended the clinic regularly. Good adherence to treatment was reported in 38.4% (n=95) and 61.6% (152) had poor compliance out of which 7.2% (n=18) never adhered to treatment. Education level did not have a statistically significant association with good compliance (p=0.613). Diabetic clinic follow up patients had better compliance (47.1%) than patients attending the hospital medical clinics (37.0%) and the private sector clinics (23.5%). Out of the patients who had poor compliance (n=152, 61.5%), 151 patients (99.3%) took lower dose of medication than recommended, 123 (80.9%) didn’t take medication on time and 122 (80.2%) didn’t understand the instructions clearly. Out of the 32 patients who were on insulin, 24 (75%) had always been compliant with treatment and only 2 (0.6%) were never compliant.

Conclusions
Drug compliance is poor in diabetic patients. However, this could be improved by giving clear instructions and motivating the patient. Limitation of this study was that we didn’t measure the blood sugar control in patients.

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Surgical aspects of thyroid and pancreatic disease
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Background
Majority of endocrine surgeries performed in a general surgical department, are related to the thyroid gland and pancreas. Even though thyroid gland enlargement is common, risk factors, aetiology, prevalence of malignancy, histological stage and benign disease related local data are not well documented.

Objectives
We looked into the data of thyroid and pancreatic surgery to identify common presentations of patients, mode of surgical management, histology and stage of neoplasm.

Methods
We analyzed data of thyroid and pancreatic surgery performed in professorial surgery department in Colombo south teaching hospital from January 2012 to April 2013 with regard to types of thyroid and pancreatic surgeries and the histology.

Results
Total of 81 patient records of thyroidectomy revealed 52% had total thyroidectomy and 48% had hemithyroidectomy and the commonest indication for surgery was for cosmetic reasons. Histology revealed benign disease in 21%, out of which 33% were hyperplastic nodules and 16% were multinodular goitres.

Malignant disease was evident in 79% of specimens which included papillary carcinoma 76%, follicular carcinoma 18%, and follicular carcinoma with micropapillary carcinoma in 6%. Majority of malignant tumours were T2 according to TNM staging system.

Total number of 12 pancreatic surgeries were analyzed and 67% was pancreaticoduodenectomy and 25% was distal pancreatectomy. Most of the pancreatic surgeries were done for malignant disease. Histology of malignant neoplasms revealed a majority of adenocarcinoma.

Conclusions
Nationwide data collection is necessary to identify the patterns and to study the aetiological factors of malignant and benign disease related to thyroid and pancreas.

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Effects of long-term metformin on neuro-physiological parameters, clinical parameters and vitamin B12 levels

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Introduction
Prevalence of type 2 diabetes (T2DM) is increasing worldwide. Most patients with T2DM are treated with metformin. Metformin is associated with vitamin B12 deficiency. Long-term metformin use could cause/exacerbate existing peripheral neuropathy.
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**Objectives**

To assess serum vitamin B₁₂ levels in patients on long-term metformin and correlate treatment parameters, clinical neuro-cognitive and neurophysiological parameters.

**Methods**

Patients with diabetic neuropathy symptoms, on metformin for >2 years, attending medical clinics of National Hospital, Sri Lanka were studied using an interviewer-administered questionnaire, modified diabetic neuropathy symptom score (m-DNS: ≥1-indicative of neuropathy) and examination score (m-DNE: >3-indicative of neuropathy), mini mental state examination (MMSE: <21-indicative of poor cognitive functions), HbA1c and serum vitamin B₁₂ levels (reference range: 200-950 pg/ml). Nerve conduction studies assessed amplitude and velocity of lower limb peripheral nerves. Data were analyzed using SPSS v20.0.

**Results**

Mean age was 62.52±7.52 (mean±SD) years (n=31, males=8; females=23). Mean duration of diabetes and metformin treatment were 11.10±7.39 and 9.26±6.66 years respectively. m-DNS (2.87±1.06) had positive correlations with metformin daily dose (1346.77±621.41mg) (rs=0.537, p=0.002) and HbA1c levels (6.29±1.63%) (rs=0.434, p=0.015). Vitamin B₁₂ levels (537.45±248.06pg/ml) were in the normal range and did not correlate with treatment parameters, m-DNS, m-DNE (6.77±2.92) or MMSE (27.13±3.66). Vitamin B₁₂ levels correlated only with amplitude of right peroneal compound motor action potential at ankle (n=25,rs=0.429, p=0.032).

**Conclusions**

Symptom scoring could be an indicator of metformin-related peripheral neuropathy and poor glycaemic control. Patients on long-term metformin had serum B₁₂ levels within normal range and inconclusive nerve conduction findings. Future studies should aim to collect data from larger samples focusing on factors which contribute to B₁₂ level in patients on long-term metformin.

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**Sleeve gastrectomy: Preliminary results from a prospective database**

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**Background**

Over the last decade laparoscopic sleeve gastrectomy (LSG) has emerged as an increasingly utilized procedure for weight loss. Apart from weight loss it can also have an impact on the obesity related comorbidities such as diabetes, hypertension and fatty liver disease.

**Objectives**

To determine the impact of LSG on weight loss, obesity comorbidities (diabetes, hypertension and fatty liver disease) and operative morbidity.

**Methods**

We performed a retrospective review of a prospectively collected database. 15 consecutive patients underwent LSG, between October 2012 and May 2013. Data including patient demographics, preoperative body mass index (BMI), pre and postoperative comorbidities, complications, and weight loss at 1, 2, 3 and 6 months, were recorded and analyzed.

**Results**

This series comprised 14 females and 01 male with a mean age of 49 (range: 31-62) years. Their mean weight was 89.1 kg (range: 73-114), and mean preoperative BMI was 36.98 kg/m² (range: 29.4-49.12). 12 patients were diabetic (80%), one patient was pre-diabetic, 8 had hypertension (53%), while 12 had fatty liver disease (80%). The mean weight loss was 9.1%, 13.1%, 16.1% and 20.4% at 1, 2, 3 and 6 months respectively while the mean BMI decreased to 33.64, 32.14, 31.03 and 28.75 kg/m² at 1, 2, 3 and 6 months respectively. Of the 12 diabetics 10 (83%) were off all anti-diabetic medication including insulin by 4 months, while the remaining two were on metformin only. 63% of the hypertensives were off all antihypertensives by 6 months respectively while the mean BMI decreased to 33.64, 32.14, 31.03 and 28.75 kg/m² at 1, 2, 3 and 6 months respectively. Of the 12 diabetics 10 (83%) were off all anti-diabetic medication including insulin by 4 months, while the remaining two were on metformin only. 63% of the hypertensives were off all antihypertensives by 6 months, while 100% of the patients with fatty liver disease improved during this period. One patient had to undergo splenectomy during the LSG and subsequently developed a gastro-cutaneous fistula which was repaired. One patient developed trocar site infection, while one had to undergo endoscopic dilatation of a stricture.

**Conclusions**

LSG is an effective surgical procedure for the morbidly obese, showing marked improvement in not only weight but also obesity associated comorbidities, shortly following surgery.
Comparison of biochemical hyperandrogenism in lean and obese South Asians with polycystic ovary syndrome

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Background

Hyperandrogenism in PCOS has diverse clinical manifestations, with obesity linked to its severe forms.

Objectives

To compare differences in clinical and biochemical hyperandrogenism among lean and overweight patients with PCOS.

Methods

Retrospective data analysis of a consecutive cohort of South Asian women diagnosed with PCOS in a specialized endocrine clinic in Colombo. They were subdivided into two groups based on their Body Mass Index (BMI) >23 Kg/m². Serum total testosterone and SHBG levels were measured and Free Androgen Index (FAI) was calculated.

Results

N= 108. Overweight/obese (n=54) and lean PCOS group (n=54) with mean age 24.6 ± 4.8 years versus. 24.5±4.7; mean BMI 28.7±5.7 kg/m² versus. 21.1 ± 1.5 kg/m² (p=0.00) respectively. Mean serum testosterone (T) 2.72 versus. 2.18 nmo/l (p=0.04). T >3.5 nmol/L occurred in 32 % of overweight PCOS versus. 21.15% of lean PCOS patients (p = 0.000). High FAI (>5) was found in 46.6% versus. 12.5% based on BMI (p = 0.043). Logistic regression analysis found BMI to be an independent predictor of elevated T with an odds ratio of 2.984 (95% CI = 2.045 - 3.922).

Conclusion

 Lean and overweight PCOS subjects have significant difference in testosterone and FAI. BMI is an independent predictor of elevated testosterone levels. Therefore, it is important to consider the BMI in the management of hyperandrogenism in South Asian subjects with PCOS.

Clinical presentation and postoperative outcome in Cushing’s syndrome: A Sri Lankan perspective

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Objective

To analyse the clinical presentation and postoperative outcome in patients with Cushing’s syndrome.

Methods

A retrospective case note analysis of 25 patients with biochemically confirmed Cushing’s syndrome in a tertiary care centre.

Results

Among 25 patients 96% (n=24) were females and 4% (n=1) were males. Mean age of presentation was 37.6 years. Weight gain (92%) was the commonest presenting feature and dorsocervical fat pad (88%) was the commonest clinical sign. Easy bruising, facial plethora, proximal myopathy and purple striae, which are more discriminatory were found in, 24%, 68%, 84% and 20% respectively. MRI pituitary demonstrated a macroadenoma in 24% (n=6), microadenoma in 48% (n=12) and no tumour in 28% (n=7). Bilateral inferior petrosal sinus sampling (BIPPS) was performed in those without a tumour and showed a ratio of >2 in 6 patients (85.7%) and <2 in one patient who was diagnosed as ectopic ACTH producing Cushing’s syndrome. Two patients (8%) had undergone bilateral adrenalectomy and 22 (88%) patients undergone transsphenoidal hypophysectomy (TSS). Post operative cure (48 hours 0900 h serum cortisol level <50 nmol/l ) was achieved in one patient who did not have a visible pituitary adenoma. 55.5% patients with a microadenoma achieved postoperative remission of hypercortisolism and 44.4% underwent radiotherapy for persistent hyper-cortisolism. In patients with macroadenoma postoperative cure and remission rates were zero and 4 underwent radiotherapy.

Conclusions

Weight gain is the commonest presenting clinical feature in Cushing’s syndrome and discriminatory features of
Cushing’s syndrome, facial plethora easy bruising and purple striae are seen less commonly in our population. In patients with microadenoma or no tumour postoperative remission rates are satisfactory but less compared to western data. In patients with macroadenoma both cure rates and remission rates are low following TSS.

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Association of physical activity with body mass index (BMI), waist circumference (WC) and visceral fat percentage among the health staff in a tertiary care setting

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Objective
To study the relationship of physical activity with body mass index (BMI), waist circumference (WC), body fat percentage and visceral fat percentage among the health staff.

Method
A descriptive study was carried out among the health staff in a tertiary care setting. Four hundred fifty two study participants were recruited representing all categories in hospital setting. An interviewer administered questionnaire was used to assess the demographic and medical history and the physical activity of the respondents. IPAQ (International Physical Activity Questionnaire) short form which was validated and translated in to Sinhala was used. Body fat and visceral fat percentages were estimated using bioelectrical impedance analysis (BIA) method and body weight, height and waist circumference were measured using WHO protocols.

Results
Half of the study population is engaged with low physical activity level (51.3%), more male staff is engaged with moderate and high physical activity (27.3% and 29.2%) compared to females (23.4% and 21%). The difference of physical activity between males and females is statistically significant (t= 2.42 p<0.05). Majority of obese staff involve in low physical activity (57.1%) and association is significant (χ²=6.8 p df=1 <0.01). There is a very poor correlation of waist circumference (r= -0.035 p>0.05) and visceral fat percentage (r= -0.031 p>0.05) with physical activity. On the other hand there is a significant inverse correlation of body fat percentage and physical activity (r= -0.1 p<0.05).

Conclusion
Females are involved in less physical activity and BMI and body fat percentages are good predictors of physical activity.

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Is ethnicity among Sri Lankan patients with diabetes, a risk factor for metabolic syndrome?

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Background
Metabolic syndrome (MetS) is associated with increased cardiovascular morbidity and mortality. Different ethnic groups in Sri Lanka have diverse cultural beliefs and dietary habits.

Objective
The aim of this study was to assess the prevalence of metabolic syndrome and the main parameters of metabolic syndrome among the patients with diabetes in different ethnic groups.

Methods
A prospective cross sectional study was carried out between May 2012 and December 2012, at the diabetes clinic of the National Hospital of Sri Lanka (NHSL). Consecutive patients with recent onset type 2 diabetes (less than 12 months) were enrolled into the study on their booking visit. Data obtained included use of antihypertensive and lipid lowering drugs, anthropometric indices, blood pressure and fasting serum lipids.

Results
391 subjects (109 males, 282 females) were included in the study. The prevalence of MetS according to the International Diabetes Federation criteria was 63.7%. Metabolic syndrome prevalence in Sinhalese, Tamil and Muslim patients were 59%, 65% and 81% respectively. There was a significant association between ethnic group and prevalence of Met S (p<0.05) and compared to Sinhalese patients, other two ethnic groups (Tamil and Sri
Lankan Moors) had higher prevalence of MetS (p<0.05). Out of individual risk factors for metabolic syndrome, only the abnormal waist circumference had a significant relationship with the ethnic groups (p<0.05).

**Conclusion**

There were significant differences with the prevalence of metabolic syndrome among the 3 main ethnic groups in Sri Lanka. Genetics and the differences in the lifestyle of these different ethnic groups are very likely to be the reasons for it.

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**Effect of addition of sitagliptin in patients with failure of traditional oral hypoglycaemic agents: A Sri Lankan experience**

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**Objectives**

Sitagliptin, a novel Oral Hypoglycaemic Agent (OHA) belonging to DPP-4 inhibitor class has been proven to be effective as monotherapy or add-on therapy in treating patients with poor glycaemic control. The aim of this study was to evaluate the effect of sitagliptin as an add-on therapy for patients with failure of traditional OHAs (metformin and sulfonylurea with or without a glitazone) in achieving glycaemic control in Sri Lankan setting.

**Methods**

This clinical audit was conducted at a private sector consultation. All patients who were commenced on sitagliptin due to unsatisfactory glycaemic control (HBA1C >7%) despite being on at least two conventional OHAs were evaluated. Data were collected both retrospectively and prospectively. Data of 105 patients are presented in this preliminary study. Data were analysed using SPSS version 16.0

**Results**

In 105 patients (mean age 55.72 (+11.58) years, males 54.8%, mean duration of diabetes 12.21 (+6.36) years) mean fasting plasma glucose (FPG) at baseline, 03, 06 and 09 months were 167.79 (+43.57) mg/dL, 126.18 (+31.12) mg/dL, 131.74 (+33.92) mg/dL and 128.66(+27.86) mg/dL respectively. Mean HbA1c at baseline, 03, 06 and 09 months were 9.05 (+1.27) %, 7.66 (+0.91) %, 7.67 (+1.05) % and 7.46 (+0.82) % respectively. A statistically significant difference was observed in both mean FPG and mean HbA1c levels at 03, 06 and 09 months when compared to baseline values (p<0.001 at each occasion). Effect on body weight did not show a significant difference at all 03 time points (p=0.26, p=0.37, p= 0.38).

**Conclusions**

Addition of sitagliptin to OHAs significantly improves HbA1c and FBG and the effects are sustainable for 09 months. There was no significant weight gain despite improvement of glycaemic control.

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**Vitamin D deficiency in Sri Lankan women: is there an epidemic?**

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**Objectives**

Vitamin D deficiency is increasingly recognized as a problem in South Asians. This has not been previously assessed in Sri Lankans. We aimed to determine the vitamin D status among women presenting with body pain not specific of any known aetiology such as arthritis or spondylosis.

**Methods**

Vitamin D status was assessed in females attending a private sector out-patient consultation with self reported non-specific bodily pain. Symptom severity was graded in a 10-point visual analog scale. Quality of life was assessed using SF-8 questionnaire.

**Results**

Among 26 participants (mean age 55.67 (+13.22) years) mean vitamin D level was 24.548 (+11.57) ng/mL. 17 (38.6%) and 19 (43.2%) participants had vitamin D deficiency and insufficiency respectively. However vitamin D status correlated poorly with symptom severity and SF-8 score.
Conclusions

Vitamin D deficiency is very common in women with non specific bodily pains. Whether this is a normal phenomenon in all women as well as men needs further studies.

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An audit on Growth Hormone Day Curves

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Introduction

The success of therapy of growth hormone(GH)-producing tumours is assessed preferably by serum Insulin-like growth factor-1. It correlates with the mean GH level in five serial samples collected during daytime (GH Day Curve-GHDC). Adequate therapeutic control is denoted by satisfying two criteria following a GHDC.

1. Mean value <5 mIU/L.
2. Two individual values <1 mIU/L1.

Objectives

1. Assess the variability of GH levels in subjects undergoing GHDC.
2. Explore the possibility of using one GH assay on pooled serum as a screening test.

Methods

Results of 83 GHDC performed at the National Hospital using an immuno-radiometric assay within 20 months, were analysed retrospectively. Agreeability of the GH level in a pooled sample made up of equal aliquots of each specimen with that of the mean GH value of the Day Curve was also looked at.

Results

1. 21(25%) satisfied both criteria, indicating adequate control.
2. 19 (23%) satisfied only criterion 1.
3. 43 (52%) did not satisfy either criterion.
4. None satisfied only criterion 2.

Variability expressed as the difference between the highest and lowest values over the mean was <1 in 81% and >2 in only 3%.

Conclusion

Individual results of GHDC showed little variability. Only those measuring <5mU/L in a pooled sample require further analysis of individual samples to confirm conformity with criterion 2. Those >5mU/L reflect inadequate control.

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Morbidity pattern of adrenocortical tumours presenting to a tertiary care paediatric center and a specialized cancer unit

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Introduction

Adrenocortical tumours are rare in childhood and adolescence. Patients can present with features of excess hormones of adrenal origin (cortisol, androgens and aldosterone). The prognostic significance of tumour size, capsular invasion and histological grade are debatable.

Objectives

1. To assess the morbidity pattern of children presenting with adrenocortical carcinoma.
2. To study the clinical presentation of adrenocortical carcinoma.

Methods

We retrospectively analyzed patients presenting to a paediatric tertiary care center and a specialized cancer unit with histologically proven adrenocortical tumours during past 7yrs. Age of onset, clinical presentation, pre and post operative adrenal hormone levels, outcome and survival were analyzed.

Results

9 patients fulfilled our inclusion criteria and all were adrenocortical carcinomas with a median presenting age
of 2 yr 8 m (range, 2 mths-8 yr). One presented with isolated virilizing symptoms leading to central precocious puberty and needed GnRH therapy. 6 had Cushinoid symptoms and 3 had both cushinoid symptoms and virilisation. Three patients with Cushinoid symptoms also had hypertension, out of which one had hypertensive encephalopathy. Six patients had complete surgical resection while 2 had residual disease. These two needed adjuvant chemotherapy and both died within 6 months after surgery. Four patients who had complete surgical excision had their endocrine abnormalities reversed clinically and biochemically (cortisol and adrenal androgens) within six months during a median follow up of two years (range, 2 mths – 5yrs).

Conclusion
Adrenocortical tumours can present with various endocrine abnormalities and complete surgical resection can reverse most of these changes. The continued follow up in a specialised unit is needed.

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Growth hormone therapy for short stature in adolescents, experience in University Medical Clinic, NHSL
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Objectives
Though growth hormone therapy is used for treatment of growth hormone deficiency (GHD) of children in Sri Lanka, its use in adolescents is not common. Our aim was to assess the response to growth hormone in adolescents with GHD in our setting presenting with short stature.

Methods
This was an observational study carried out at University Medical Clinic of NHSL. Adolescents presenting with short stature over a period of 2.7 years were investigated with IGF-1, Insulin tolerance test (ITT), bone age and commenced on growth hormone therapy. They were monitored with anthropometric measurements, IGF-1 and observed for side effects.

Results
Among the 21 adolescents, 15 were males (71.4%). Mean age, height, weight at presentation were 15.0 (10.4-19.1) years, 138.6 (+ 7.6) cm and 38.4 (+13.0) kg respectively. Patients were followed up for 1.3 (+0.8) years.

Low IGF-1 was found in 16 (76.1%). IGF1 was normal in 4 Turner patients (n=5). Failed ITT was found in 13 (81.3%; n=16) and was discontinued in one due to hypoglycaemia. Mean growth velocities were 7.7 (+4.4) cm/year and 9.1 (+2.0) cm/year for patients who failed and passed ITT respectively. In those with failed ITT, no significant correlation was found between age, bone age at commencement of therapy and growth velocity.

Girls with Turner syndrome (n=5) showed a mean height velocity of 5.9 cm/year following GHT.

Side effects were complained by 3 (14.9%) patients which were diabetes mellitus (n=2) and carpal tunnel syndrome (n=1).

Conclusion
GHT is usually a safe treatment and is useful in achieving satisfactory height gain in adolescents with short stature.

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Evaluation of the accuracy of glucometers currently used in Sri Lanka
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Introduction and objectives
Self monitoring of blood glucose using a glucometer has been shown to be effective in improving glycaemic control in diabetic patients. However, the studies done in other countries have shown a significant variability with the accuracy of glucometers. Although the glucometers are being used in our clinical practice, there is limited data regarding the accuracy of these meters in our clinical setup. This study aimed to assess the accuracy of commonly used glucometers in Sri Lanka.
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Methods

Commonly used glucometers were identified (N=8, A-H). Healthy volunteers and patients admitted to the National Hospital of Sri Lanka were selected by convenient sampling (n=50, 34 patients, 16 healthy volunteers) after informed consent.

A venous sample (VS) of blood glucose from each subject was analyzed using a standardized method and taken as the reference point. Concurrent finger-prick (FP) values were determined using all glucometers ensuring uniformity.

Results

The range of glucose measurements was 69 – 448 mg/dl. Mean difference (mg/dl) between VS and FP values for glucometers with 95% Confidence Interval and P values according to ascending order were F 1.78 (-6.48,+10.04), P=0.667; A 6.96 (-11.66,-2.25), P=0.005; C 7.92 (+1.43,+14.40), P=0.018; E 10.20 (-17.19,-3.20), P=0.005; H 13.66 (-20.40, -9.91), P<0.001; B 17.42 (-23.78,-11.05), P<0.001; G 18.16 (-25.07, -11.24), P<0.001; Highest concordance with American Diabetes Association (ADA) recommendation of less than 5% bias was seen in ‘F’ and lowest in ‘G’. None of the glucometers manage to achieve the ISO recommendation but highest concordance was seen in ‘E’ and lowest in ‘B’.

Conclusions

A statistically significant difference between VS and FP values were noted in the majority of glucometers. The concordance with ADA recommendation seems unsatisfactory in majority.

Aldosterone secreting adrenocortical carcinoma

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Introduction

Adrenocortical carcinomas (ACC) are uncommon. The incidence is approximately 0.6-1.67 cases per million persons per year. It occurs in 2 major peaks, in the first decade of life and again in the fourth to fifth decades. Functional tumours are more common in children, while non functional tumours are more common in adults.

Nonfunctional tumors account for approximately 40% of patients with ACC and typically present with fever, weight loss, abdominal pain, back pain and abdominal fullness, or symptoms related to metastases.

The hormonally active variants of ACC constitute approximately 60% of cases. Approximately 30-40% of adult patients present with the typical features of Cushing syndrome, while 20-30% present with virilization syndromes. In children, however, more than 80% present with virilization syndromes.

Other modes of presentation include profound weakness, hypertension, and/or ileus from hypokalemia related to hyperaldosteronism.

Case report

A 30 year old lady presented with generalized body weakness and high blood pressure. Examination showed right upper abdominal mass and no features suggestive of hormonal excess or deficiency and investigations revealed persistently low potassium levels. Imaging studies showed a large right adrenal mass. Her 24 hour urinary VMA levels (twice), overnight dexamethasone suppression test and other basic investigations were normal. Her aldosterone level was very high. The aldosterone/renin ratio was significantly very high (1875). There was no evidence of metastasis.

She had undergone surgery and histopathology report showed a high grade tumour with necrosis, capsular and vascular invasion suggestive of adrenocortical carcinoma. Regional LNs were present and pathologically staged as PT 3. (tumour of any size, locally invasive but not involving adjacent organs).

We are waiting for the Ki 67 and other specific staining reports. Postoperatively, her blood pressure and serum electrolytes were normal without any drugs and aldosterone level became normal. She is under care of oncologist now and they plan to start local chemo and/or radiotherapy in near future.

Discussion

Eventhough adrenocortical carcinoma is rare, clinicians should think of it as a differential diagnosis when a hypertensive patient presents with hypokalaemia and a suprarenal mass. Primary hyperaldosteronism associated with ACC is very rare (2.5%) and this is the first reported case of aldosterone secreting ACC in Sri Lanka.
Prevalence of colonic polyps among patients with acromegaly

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Background

Patients with acromegaly are reported to have a higher prevalence of colorectal adenoma, which is a pre-malignant condition. It has been recommended that patients with acromegaly should undergo colonoscopic surveillance to detect these lesions early.

Objectives

Our objective was to evaluate the prevalence of colonic polyps in patients with acromegaly.

Methods

This was a descriptive cross sectional study conducted in the Endocrinology and Pituitary clinics at National Hospital of Sri Lanka between January 2012 and June 2013. From a total of 72 patients with acromegaly, 33 patients (13 males and 20 females), who underwent colonoscopy were enrolled for analysis. Age group of this sample was 29 to 71 years. None of these patients had previous or family history of colonic neoplasm or colonic surgery.

Results

The mean age of the patients at diagnosis was 40.12 (SD±11.9) years and average lag time between symptomatology and diagnosis of acromegaly in these patients were 3.5 (SD ± 2.8) years. The basal mean plasma GH was 57.91 mU/L (SD±53.74) and on imaging 28 (84.84%) had macroadenomas.

Colonoscopic examination was complete to the cecum in 23 patients (69.69%), to the splenic flexure in eight patients (24.24%) and to hepatic flexure in the remaining two patients (6.06%). Colonoscopy findings were abnormal in 11 (33.33%) patients. Five patients with acromegaly had polyps in their colonoscopy in which two of them had tubular adenoma with low grade dysplasia. The group of acromegalic patients with and without polyps did not differ significantly in age 39.8±13.3 years vs 39.71 ±11.34 years, (P=0.326), in duration of disease 2.8±2.0 years vs 3.6±3.0 years, (P=0.544) or in circulating basal GH levels (77.13 ±64.91mU/L vs 42.61±42.70 mU/L, P= 0.134). Diabetes did not influence the prevalence of colonic polyps in acromegaly. Having polyps was statistically significantly higher among male sex than female sex (P<0.05), but a conclusion cannot be made due to small sample size. Four out of the 5 acromegalic patients who had polyps had active disease when the colonoscopy was performed.

Conclusion

Despite lower prevalence of colonic polyps (15%) compared to studies from west we still found premalignant lesions in 2 patients (6.06%).

Hypoglycaemia: A descriptive study of causes...

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Objectives

Hypoglycaemia is a feared experience for diabetic patients due to the disturbing symptoms which reduces compliance with drugs and also contributes to the increased morbidity and mortality. Identifying the cause of hypoglycaemia is pivotal for optimal glycaemic control. We intended to describe common causes and risk factors for hypoglycaemia among Sri Lankan diabetic patients.

Methods

An audit was conducted using a structured, interviewer administered questionnaire among 1000 diabetic patients attending a private sector clinic using consecutive sampling. Hypoglycaemic episodes during the preceding month were inquired and severity was graded on clinical features and capillary blood glucose levels.

Results

In 1000 patients (mean age 54.97 (+12.48) years), males 58.6%, mean duration of diabetes 10.61 (+8.10) years, mean
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FBS and HbA1c were 134.55 mg/dL (+50.19) and 7.82% (+1.71) respectively. Prevalence of hypoglycaemia was 26.1% (mild 20.7%, moderate 3.9%, severe 1.5%). Sudden change in the diet (quantity, composition or timing) was noticed in 46.7%, increased medicine dosage in 16.9% and unaccustomed exercise in 15.7% were the commonest causes. A cause was not recognized in 16.3%. In this study, 16.9% of patients recognized non prescribed native food as the probable cause for hypoglycaemic episode (Thebu 52.3%, Karawila 54.5%, Kothalahimbutu 11.4%, Madatiya kola 4.5%, Kowakka 6.8%).

Conclusions
Hypoglycaemia is common among diabetic patients. Patients need advice to maintain a regular routine of diet and exercise. Consumption of non-prescribed native food should be specifically looked into as a probable cause for hypoglycaemia.

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A study to compare the effects of a new generic product of methimazole with carbimazole on biochemical parameters in Graves’ hyperthyroidism


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Objectives
Carbimazole (CBZ) and methimazole (MTZ) are proven to be effective in achieving euthyroidism in patients with Graves’ hyperthyroidism. The aim of this prospective randomized clinical trial was to establish non-inferiority of the biochemical and clinical effects of a locally manufactured methimazole which was introduced to Sri Lanka recently, in comparison to carbimazole. Preliminary data are presented in this on-going study.

Methods
Patients (n=15) who were clinically and biochemically diagnosed with Graves’ hyperthyroidism were randomized to receive MTZ (n=6) and CBZ(n=9). Biochemical and clinical parameters were monitored at 0,4,8 and 12 weeks. Drug doses were titrated according to a standard protocol. Results were analyzed using independent sample t-test using SPSS version 16.0.

Results
There was no statistically significant difference in mean baseline FT4 levels between MTZ and CBZ groups (p>0.05). In both groups, there was a significant reduction in mean FT4 levels at 04 weeks and at 12 weeks compared to the baseline FT4 levels (p<0.01).At 04 weeks and 12 weeks of treatment, mean reductions of FT4 levels in MTZ group were 2.05 ng/dL (±0.734) and 3.177ng/dL (±0.58) vs2.155ng/dL (±1.19) and 2.59ng/dL (± 0.837) in the CBZ group at corresponding time points respectively. There was no statistically significant difference in the two groups at 04 and 12 weeks (p=0.399 and p=0.137 respectively). Adverse drug events were not reported in either group.

Conclusions
MTZ and CBZ are both effective and MTZ is non-inferior to CBZ in reducing the hyperthyroxinaemia in patients with Graves’ disease.

Abbreviations - FT4- free T4, FT3- free T3, TSH- Thyroid stimulating hormone.

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Body fat and visceral fat percentages as predictors of cardiovascular risk and obesity

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Objectives
To stratify the cardiovascular risk and study the relationship with body fat percentages, and to study the relationship between body mass index (BMI) waist circumference (WC), body fat percentage and visceral fat percentage among health staff.
Methods

A cross sectional study carried out among the health staff in a tertiary care setting. 452 study participants were screened among all categories of health staff. Body fat and visceral fat percentages were estimated using bioelectrical impedance analysis (BIA) method. Cardiovascular risk was calculated using Framingham’s cardiovascular risk score.

Results

According to the BMI, 35.4% (n=57), 8.7% (n=14) males and 41.9% (n=122), 15.5% (n=45) females were overweight and obese. Based on body fat percentage obesity was 63.4% (n=102) and 65.6% (n=191) among males and females respectively. Central obesity was 23% (n=37) and 62.2% (n=168) according to the WC among males and females respectively. In females BMI showed the strongest correlation with visceral fat percentage (r=0.846, p<0.001) than WC (r=0.722, p<0.001) and body fat percentage (r=0.558, p<0.001). In males although correlations with BMI was weak, WC (r=0.2, p<0.01) showed the strongest correlation with BMI compared to body fat percentage(r=0.191, p<0.01) and visceral fat percentage (r=0.16, p<0.01). Ten year cardiovascular risk was > 10% in 7.69% (n=9) males and 4.54% (n=9) females. In females cardiovascular risk showed significant correlation with BMI, visceral fat and body fat percentages (r= 0.208, 0.295, 0.293, p<0.01). In males significant correlation was seen with visceral fat percentage (r=0.238, p<0.01).

Conclusions

Obesity prevalence is higher among studied health staff compared to normal population. BMI is a good predictor of visceral obesity in females while WC is the best predictor in males. Eventhough it is weak, cardiovascular risk showed significant correlation with visceral fat percentage.