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VIEWPOINT

JIACM 2013; 14(3-4): 202-3

Inventing diseases to sell drugs

*BM Hegde**

"Honesty is the best policy. If I lose mine honour, I lose myself."

– William Shakespeare (1564-1616).

I have known of many tricks of the trade of the pharmaceutical lobby but not this one till very recently – although I had a hunch that this could be there. At the same time I am happy that there are people with some conscience pricking them before death at least. Here is a nice story. Of late when one opens any newspaper or journal, there are articles on a recent disease in children by name ADHD (Attention Deficit Hyperactivity Disorder) and our paediatricians bend over backwards to make the diagnosis and start our innocent children on dangerous chemical drugs at that tender age. Now comes the bombshell. The 87-year-old American psychiatrist, Dr. Leon Eisenberg, made a statement to the German magazine *Der Spiegel*, a couple of months before his death that ADHD is a fictitious disease which they put together for the benefit of drug companies in the new disease classification in the American Psychiatry Association's DSM (Diagnostic and Statistical Manual of Mental Diseases).

I only hope that many other disease inventors will also come clean before they die to clear their conscience before "moving beyond". Professor Jerg Blech, another German, had written a beautiful book 'Inventing Diseases' where he gives a graphic description of hypertension having been discovered as a disease needing drug treatment through the German plan of 'Well Man' clinics in nice air-conditioned vans with beautiful nurses, parked around church squares and shopping malls to give people a 'Free' check-up, a dangerous activity when one feels healthy and happy. Any one that walks in, becomes a patient. Actually it was Leon Eisenberg who once asked his new brilliant resident as to who is a patient? Pat came the reply: "A man/woman who sees any doctor becomes a patient!" What rattled Leon further was the answer to his second query: When does that person become normal again? "Rarely ever, if ever, was the answer." May be this is the reason that tickled his conscience.

There is no proof or test to find out exactly what chemicals are "out of balance" in the brain for ADHD or any other disorder. Most of those drugs are unnecessary as they are known to provoke suicide and homicide. "Since that DMS conference in 1968, Dr Eisenberg's contribution to mental disease by invention and committee consensus has resulted in drugging millions of children from preschool age through high school. It is currently estimated that up to 20% of children from nursery school and kindergarten through high school and in foster homes have been prescribed Ritalin. Ritalin, commonly prescribed for kids 'diagnosed' or better still, labelled with ADHD, was tested a little over a decade ago by the Brookhaven National Laboratory (BNL). The BNL study determined that "Ritalin is pharmacologically similar to cocaine with perhaps even worse brain damaging potential," writes Mike Adams in his recent blog. Dr Irwin Savodnik, Assistant Clinical Professor of Psychiatry at UCLA School of Medicine, California, USA, was of the opinion that "The very vocabulary of psychiatry is now defined at all levels by the pharmaceutical industry." This racket has been going on ever since and has been able to get even health insurance to cover their dark deeds.

Vaccination is another fertile ground for the pharmaceutical industry where most of what they sell has dubious value. The lead researcher, Dr Diane Harper, who was instrumental in creating Gardsil, and Cervarix, admitted back in 2009 that the vaccines were essentially useless and more dangerous than the very conditions they were hailed as preventing and treating? A 2009 article published by *CBS News* – in fact – which is still available online, reveals the truth about these vaccines.

One particular quote, which was pulled up using the Way Back Machine, reveals both Gardasil and Cervarix do nothing to prevent cervical cancer, which is their primary claim to fame. "The rate of serious adverse events (from Gardasil) is on par with the death rate of cervical cancer," admitted Dr Harper at that time, refuting a pro-Gardasil piece published by Slate. "Gardasil has been associated with at least as many serious adverse events as there are deaths from cervical cancer developing each year. "Dr Harper dropped a bomb when she told reporters that the

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public health benefit of getting vaccinated with Gardasil "is nothing," adding that the vaccine has led to "no reduction in cervical cancers." She quickly withdrew her statements saying that the media had distorted her story – almost on the lines of Indian politicians.

Dr Harper went on to admit that deaths from Gardasil have been underreported by the US Centres for Disease Control and Prevention (CDC), which has given the illusion that the vaccine is somehow safe. The vast majority of HPV infections resolve themselves on their own within a year, and nearly all of them within two years. She also admitted that an extremely small number of people experience symptoms from infection. Millions of young girls and now even boys, some as young as nine years old, have received the vaccine since 2006. Some of what she had said then is still on line.

Recently Dr Puliyal from New Delhi – an expert in this field – had exposed the myth of another childhood vaccine, the pentavalent vaccine. But that does not seem to stir the conscience of our greedy powers that be! Years ago, in 1999 or so, Dr Prem Bhargava, the then Vice-Chairman of the Indian Knowledge Commission, resigned from his job as he had serious reservations about oral polio vaccine for malnourished children. When I had just retired from the Vice-Chancellor's post in 2003, the then Deputy Commissioner of Udupi district wanted me to retract an article of mine on polio dangers for malnourished children, which information, by then, had even entered the British Pharmacopoeia. As I refused to do that, he made my colleagues in the University to release a paper statement that I "had forgotten my medicine and people should not give heed to my article as the whole Manipal University was fully with the government in vaccinating even the malnourished children!" They obliged him, may be some quid pro quo in return for some favours from the government. I cannot but pity those statements and our commitment to truth in medical science.

We can go on and on till the cows come home on the fraud in medical research, but I highly recommend the following article in *The Atlantic* magazine of November 20th, 2010 by Davis Freedman on the important topic:'Lies, Damned Lies and Medical Research'. The article is the result of a long interview with Professor John PA Loannidis of Stanford University who recently has been pioneering the work to expose these frauds very successfully. John is a much respected member of the American medical scene. A couple of quotes from that article are worth mentioning here below.

"Even if changing that one factor (risk) does bring on the claimed improvement, there's still a good chance that it won't do you much good in the long run, because these studies rarely go on long enough to track the decades-long course of disease and ultimately death. Instead, they track easily measurable health "markers" such as cholesterol levels, blood pressure, and blood-sugar levels, and meta-experts have shown that changes in these markers often don't correlate as well with long-term health as we have been led to believe. On the relatively rare occasions when a study does go on long enough to track mortality, the findings frequently upend those of the shorter studies. (For example, though the vast majority of studies of overweight individuals link excess weight to ill health, the longest of them haven't convincingly shown that overweight people are likely to die sooner, and a few of them have seemingly demonstrated that moderately overweight people are likely to live longer.)!" Is anyone of you surprised by these revelations? I am sure not. Who wants to bell the cat, though?

"Honesty is the best policy when there is money in it."

– Mark Twain (1835-1910).

"Before old age my care was to live well;
in old age, to die well."

– Seneca.

ORIGINAL ARTICLE

JIACM 2013; 14(3-4): 204-8

Serum elastin and 25 hydroxyvitamin D levels in women with pelvic organ prolapse

Swati Sharma, Neerja Goel**, SV Madhu***, Shalini Rajaram**, Satendra Sharma*****

Abstract

Introduction: Operative procedures for pelvic organ prolapse (POP) have increased in the last two decades. Aetiological basis need to be readdressed as further increase by 45% is estimated in the next 30 years.

Aims: This study was conducted to estimate the levels of elastin and 25 hydroxyvitamin D (25 OH Vit D) in serum of patients with POP and controls, correlating them with the degree of prolpase and modified vaginal health index (MVHI).

Materials and methods: Thirty postmenopausal women with POP were selected and thirty postmenopausal with no prolapse served as controls. A detailed history was taken. General examination, systemic examination, and MVHI was done for all the women under study. Women with prolapse underwent traditional anatomical examination of prolapse followed by pelvic organ prolapse quantification. Serum 25 OH Vit D levels were determined with radioimmunoassay. Elastin concentration in serum was measured using enzyme linked immunoassay.

Results and conclusion: Controls had mean Vit D of 14.5 ng/ml compared to cases where mean was 11.8 ng/ml (p = 0.481). BMI showed an inverse association with Vit D (p = 0.93). Positive correlation was seen between Vit D and MVHI (p = 0.046). Elastin was significantly more in the study group compared control (p = 0.001). Borderline increase in elastin was observed with increasing stage of POP (P = 0.086). Elastin metabolism is increased in POP and increases further with the stage of POP. Although no conclusion can be made on the effect of Vit D on POP but possibility of it being a causative factor cannot be ruled out. Vit D therapy can improve tissues quality. This study underscores the need for further consideration of elastin and Vit D as potentially new modified risk factors for POP.

Introduction

International Continence Society defines pelvic organ prolapse (POP) as downward descent of the pelvic organs, which results in protrusion of the vagina and/or uterine cervix and does not include rectal prolapse[1]. More than 11% of women require surgical correction of prolapse in their lifetimes[2]. With the growing aged population in the country, postmenopausal health problems and needs are likely to become a great challenge to public health.

The aetiology of POP is multi-factorial. Pregnancy, increased age, increased BMI, raised intra-abdominal pressure, and chronic cough have been reported as major causes of prolapse. Higher body mass index (BMI), chronic straining, obstructive lung diseases, oestrogen deficiency, previous surgeries for prolapse, or hysterectomy[2,3,4] have been shown to be important risk factors in some studies. Connective tissue abnormalities, congenital or during child birth trauma, have shown a causal relationship[3].

A large number of deliveries in India are conducted without proper supervision and there are no provisions for good antenatal and postnatal care. As medical facilities are sparse in far flung rural areas, complications of POP are common in our country. Moreover, to date, there are no effective therapies to prevent progression of POP[4]. An understanding of factors that lead to both the onset and progression of POP will not only help improve the treatment, but may also contribute to the development of prevention strategies.

To date, a unifying theory explaining the cause of pelvic organ prolapse based on objective scientific data does not exist. With increasing research, various previously unknown aetiological factors have come to light: vitamin D and elastin being a few to name. There is a paucity of research in this field, and literature found had contradictory results.

Connective tissues, consisting mainly of collagen and structural glycoproteins are an important part of the supportive structures of the genitourinary region. Connective tissue undergoes constant turnover and remodelling in response to stress and this process is affected by hormonal changes that occur during pregnancy and parturition as well as ageing. Lack of oestrogen following menopause results in decompensation in the repair mechanism of cardinal

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ligaments. This is probably due to changes in elastin-binding protein in fibroblasts[5].

Elastin is an extracellular matrix protein that is responsible for properties of extensibility and elastin recoil in the tissues. Physiologically, elastin is one of the most stable proteins in the body. However, the female reproductive tract is unique in that elastin does turnover throughout the reproductive stage of the female lifecycle. We therefore sought to compare serum elastin metabolism in women with and without POP.

Vitamin D insufficiency or deficiency is epidemic among adults. Vitamin D is also an independent factor in POP. In previously done studies and surveys, pelvic floor disorders have been linked to osteoporosis and low mineral density[6]. Another study showed association between vitamin D levels and left leg muscle strength[7]. Thus it is possible that low vitamin D contributes to the development of poor muscle strength and leads to pelvic floor disorders.

Elastin metabolism is modulated by steroid hormones and is dependent on calcium[8]. Vitamin D_3 is involved in the regulation of calcium metabolism and influences the expression of various extracellular matrix proteins. Tropoelastin expression is downregulated by exposure to 1,25 vitamin D3 by post-transcriptional mechanism[8]. Thus it is possible that decreased vitamin D leads to altered elastin metabolism leading to POP. Therefore we decided to correlate elastin and vitamin D. In earlier studies, elastin levels were done on vaginal tissue; this made it difficult to find healthy controls as biopsy was required. Moreover, elastin levels in vaginal tissue could be affected by local pressure changes. To overcome these shortcomings it was decided to estimate elastin levels in serum.

Aim

To estimate the levels of elastin and 25 hydroxyvitamin D in serum of patients with POP and compare them with controls.

Objective

To correlate the levels of elastin and 25 hydroxyvitamin D with the degree of prolapse.

To correlate the effect of elastin and 25 hydroxyvitamin D levels on modified vaginal health index.

Materials and methods

This was a comparative study conducted in the Departments of Obstetrics and Gynaecology, Medicine and Pathology, UCMS and GTB Hospital, Delhi from November 2010 to April 2012. Thirty postmenopausal women presenting in the OPD with uterovaginal prolapse were randomly selected. Thirty controls were enrolled – all were postmenopausal females with normal pelvic support.

Each subject was selected after fulfilling the exclusion or inclusion criteria. Inclusion criteria was postmenopausal women and age ranging 40 years and above. Exclusion criterias were connective tissue disorders, osteomalacia, rickets, and previous surgery for prolapse or hysterectomy, women on vitamin D or calcium supplements. Written informed consent was taken after explaining the nature and purpose of the study.

Women participating in the study underwent a detailed history and examination. Modified vaginal health index was calculated for both cases and controls. Seven parameters are included in modified vaginal health index. Each parameter is graded from 1 to 3, and total score ranges from 7 to 21. The lower score has greater vaginal atrophy and vice versa.

Table I: Modified vaginal health index[9].

Parameters	1	2	3
pH	> 6.5	5 - 6.5	< 5
Moisture/ consistency	No moisture	Minimal moisture/ superficial layer of scanty thin white mucous	Normal moisture/ with flocculent fluid
Rugosity	None	Minimum	Good
Elasticity	Poor	Fair	Excellent
Length of vagina	< 4 cm	4 - 6 cm	> 6 cm
Epithelium integrity	Petechiae present	Petechie after scraping	Normal, not friable
Vascularity	Minimal	Fair	Good

pH was noted by litmus paper kept in the vagina for 1 minute and the colour compared to standardised colours. Moisture/consistency of the fluid was measured by putting the vaginal fluid on a clean glass slide for grading. Rugosity and elasticity were assessed by inspection and palpation of vaginal mucosa by the index finger. Length of the vagina was measured by the index finger and Ayre's spatula from the highest point in the vagina till the vulval outlet. The mean of the two measurements was taken as average length. Epithelial integrity was assessed by presence of petechiae on the vaginal wall by pressure of index finger. Vascularity was assessed by inspection of the colour of the vagina.

Local examination was done SUI was looked and levator muscle tone was assessed. Prolapse was examined and quantified according to the traditional anatomical site

prolapse classification, followed by pelvic organ prolapse quantification, and stage of POPQ was assigned. Pelvic organ quantification as described by International Continence Society was done.

Serum was retrieved after total sample collection. Vitamin D and elastin was measured in the serum. Diasorin's radioimmunoassay (RIA) method was used to measure 25 hydroxyvitamin D levels. Elastin levels were measured by ELISA with Human Elastin, ELN kits.

Results

Women in this study ranged from 40 - 85 years. Mean age of the participating women was 58.6 ± 8.52 years. Both the groups were comparable with respect to age. Average age at first childbirth was 21.4 years. Almost all the deliveries were home deliveries by untrained dais. Weight of the baby was not recalled by most. Median parity in the study was 5. Median parity for control group was 4, and for cases 5. There was statistically no significant difference between the two groups. Average menopausal age was 14.5 ± 7.60 years in cases and 9.5 ± 6.20 years in controls. Both the groups were comparable without any statistical difference. The most common presenting complaint was something coming out of the vagina and heaviness in the perineum. Other complains were backache (90%), difficulty in reducing the prolapse (90%), pain in abdomen with dragging sensation (43%), dyspareunia (37%), vaginal itching (10%), urinary complaints (40%), and stress urinary incontinence (23.33%). Nobody complained of bowel symptoms. Average BMI was 22.27 ± 2.56 kg/m^2; both the groups were comparable.

Mean of modified vaginal health index for cases was 12.67 ± 2.721 and for controls was 13.40 ± 2.5. Controls had better MVHI score compared to controls but this was not significant (p value = 0.281). MVHI was seen decreasing significantly with increase in age and menopausal age (P value 0.002). Most of the subjects had stage III prolapse (63.33%), stage I (10%), stage II (10%), and stage IV (16.66%). No association was found between stage of POP and age, P value was 0.321. Stage of POP had inverse correlation with MVHI. Correlation coefficient was -0.448 and P value was 0.013 which was statistically significant.

Vitamin D: Values of vit D between 30 - 80 ng/ml were taken as sufficient, less than 30 ng/ml as insufficiency, and deficiency as less than 10 ng/ml. All the women had vit D less than 30 ng/ml. In the POP group mean was 11.914 ± 6.217 ng/ml, and among controls the average was 14.584 ± 7.298 ng/ml. There was an insignificant increase in vitamin D values in controls, P value was 0.133. This was in accordance to our hypothesis that vitamin D is less in women with prolapse.

Table II:

Vitamin D	No. of patients in study group	Percentage	No. of patients in control group	Percentage
< 10 ng/ml	10	33.33%	7	23.33%
10 - 20 ng/ml	17	56.66%	18	59.99%
20 - 30 ng/ml	3	10%	5	16.66%

Among patients with stage I prolapse, all had value more than 10 ng/ml compared to only 40% among stage IV which had vit D more than 10 ng/ml. In stage II, 67% had values more than 10 ng/ml. In 69% of patients with stage III prolapse, value of vit D was found to be more than 10 ng/ml. Association was statistically insignificant with P value being 0.481. Calculation was done using Fisher exact test.

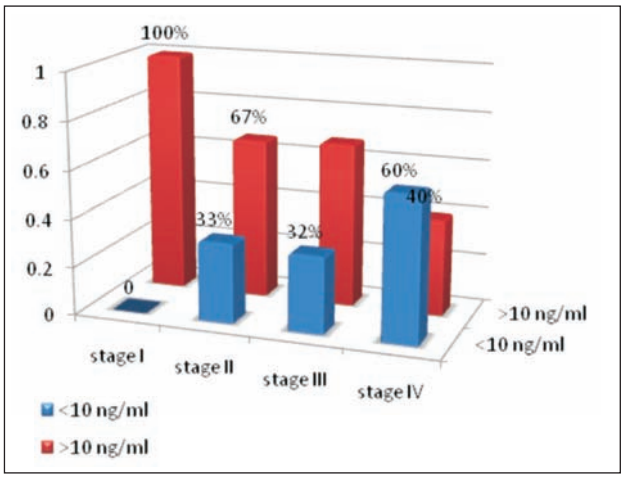

Fig. 1: *In earlier stages Vit D is mostly more than 10 ng/ml. In stage 3 and 4, values were mostly less than 10 ng/ml.*

More subjects became deficient in vit D with increasing age. The association was found to be statistically insignificant (P value 0.589). There was a visible increasing trend in vit D deficiency with increase in time since menopause (P value 0.283). In patients with BMI < 18.5 kg/m^2, only 29% patients were vit D deficient as compared to 68% in group with BMI > 25 kg/m^2. Using chi-square test, this association was found borderline significant with P value 0.093. With increase in vitamin D level, the modified health index improved. There was positive association with correlation coefficient being 0.259, P value was 0.046 which was statiscally significant.

Elastin: Elastin in the study group was more than in control group. A statistically significant association was seen. Mean for the study group was 11.18 ± 8.01 ng/ml. Average for the control group was 5.13 ± 4.48 ng/ml. P value was 0.001. A statistically significant difference was seen which was in accordance to our hypothesis that in POP, elastin metabolism is increased.

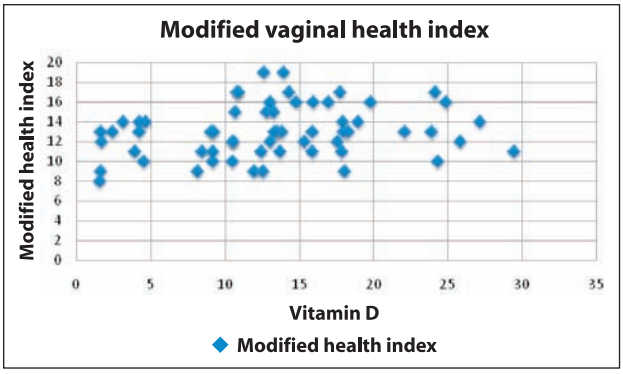

Fig. 2: *Towards the left of the graph MVHI is also low. It is visible that women with vitamin D value less than 10 ng/ml had less modified health index score.*

Table III:

Group	Mean	Std. deviation	Std. error of mean	P value
Study	11.18	8.01	1.46	0.001
Control	5.13	4.48	0.81	

Elastin and vitamin D had no correlation. Elastin failed to show any correlation with MVHI. Correlation coefficient was 0.015 and significance was 0.907. Elastin was seen to increase with increase in stage of prolapse. Borderline significance with correlation coefficient of 0.318, and P value of 0.086 was found.

Discussion

In this study MVHI was seen to deteriorate significantly with increase in stage of POP. Correlation coefficient was -0.448 and P value was 0.013. It shows vaginal tissues wear out with increasing prolapse.

In our study, all the women had vitamin D less than 30 ng/ml. In the study by Badalian and coworkers, 82% had vit D less than 30 ng/ml; this study was US-based where the nutritional status of patients is better than ours[8]. Among studies on post-menopausal women without osteoporosis or musculoskeletal diseases with cut-off of 20 ng/ml, vitamin D inadequacy ranged from 1.6% to 86%[10,11]. In the present study, 86.6% patients had vitamin D less than 20 ng/ml.

The controls had a mean vitamin D level of 14.5 ng/ml compared to cases which had a lower mean of 11.8 ng/ml. This was consistent with our hypothesis but difference was not statistically significant. This could be because of the small study size. Vitamin D deficiency was seen in more women with higher stage of POP compared to lower stage, but association was statistically insignificant with P value being 0.481. In the present study, most of the women had stage III prolapse and women in other stages were quite less; this could be the cause for statistically insignificant results.

Old age (> 70 years) was associated with a higher prevalence of vitamin D inadequacy in a previous study by Gaugris *et al*[12]. In the present study, vitamin D levels decreased with increasing age. Similar results were seen in a study by Badalian and Paula; in both the studies statistical significance was not found[6].

BMI showed an inverse association with vitamin D: those with higher BMI had lower vit D levels. Borderline significance with P value 0.93 was found. Similar patterns were found in previous studies by Badalian *et al*[6]. With increasing vitamin D levels, significant improvement in modified vaginal health index was observed. P value was 0.046. Vitamin D has positive impact on vaginal tissues.

In our study, elastin was significantly more in the study group compared to controls, P value was 0.001. This was in accordance to previous studies which say elastin metabolism is increased in POP (Zong and colleagues, Moalli and co-workers, and Strinic *et al*[5, 13, 14]).

In a study by Zong and co-workers, tropoelastin (432%), mature elastin (55%), proMMP-9 (90%), and active MMP-9 (106%) were increased in women with prolapse relative to those in the control group while active MMP-2 (41%) was decreased[7].

Strinic *et al* found a significant increase in MMP-1 immunohistochemical expression in uterosacral ligament tissue from women with POP (P=0.029). In contrast, there was no difference in immunohistochemical expression of MMP-2 between women with POP and those without (P=0.899)[13].

Moalli with co-worker found that there was no difference in the expression of proMMP-2, active MMP-2, or proMMP-9; however, active MMP-9 was increased in patients with prolapse (P = .030). The increase in active MMP-9 expression in the vaginal tissues of patients with prolapse suggests that this tissue is actively remodelling under the stresses associated with prolapse[14].

Klutke *et al* found significantly decreased desmosine content in uterosacral ligament tissue from women with prolapse versus controls. Suppression of mRNA for Lysl oxidase (LOX) and two LOX isoenzymes was correspondingly present. These results suggest that altered elastin metabolism is present in uterine prolapse[15]. Borderline increase in elastin was observed with increasing stage of POP, p value was 0.086.

Older women had significantly lower modified health index in comparison to younger females who had higher modified health index. Correlation coefficient was -0.395 and P value was 0.002 which is clinically significant. MVHI and menopausal age showed statistically significant association. Correlation coefficient was -0.389, P value was

0.038. With each passing year after menopause, modified health index keeps on deteriorating.

Conclusion

In this study, postmenopausal women with POP were compared with postmenopausal women without POP. Vitamin D was found to be decreased in both the groups. Women with POP had mean vitamin D lesser than control group. Vitamin D was also seen to decrease with increasing age and stage of POP, but statistical significance was not found. Vitamin D was seen to decrease with increase in BMI significantly. Vitamin D was also seen to have positive impact on vaginal tissues as it improved MVHI. Possibility of vitamin D being a causative factor for POP cannot be ruled out. Vitamin D therapy can improve vaginal tissues quality.

Elastin metabolism is increased in POP and increases further with increase in stage of POP. No association was found between vitamin D and elastin. In this study, we assessed only the mature form of elastin and not the precursor tropoelastin whose metabolism is regulated by vitamin D. This could be the reason for lack of correlation in the study. In this study we assessed only vitamin D and mature elastin. A larger study assessing vitamin D, bone mineral density, calcium levels, and mature elastin with its precursors and metabolising enzymes need to be carried -out to establish a strong and definitive association.

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"Pain is life – the sharper, the more evidence of life."

– Charles Lamb.

ORIGINAL ARTICLE

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Prevalence and surgical outcomes of varicose veins at Regional Institute of Medical Sciences, Imphal

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Abstract

The prevalence and incidence of varicose veins of lower limb are common in Manipur. During a study period of ten years (2001-2010) at Regional Institute of Medical Sciences (RIMS), Imphal, Manipur, 432 cases of varicose vein had attended the outdoor of the Cardiovascular and Thoracic Surgery Department of the institute. Pre-operative Doppler study of the varicose veins was done as routine procedure. Eighty patients had undergone operation. Patients were checked-up in the OPD regularly every 3 months in the first year of the post-operative period. Long saphenous vein reflux was more completely abolished by combining stripping with saphenofemoral junction ligation.

Key words: Varicose vein, stripping long and short saphenous veins, paraesthesia, recurrence.

Introduction

According to the World Health Organisation, varicosities are defined as saccular or cylindrical widened superficial veins, where the widening may be circumscribed or segmental. In general, the dilatation of the veins is associated with tortuosities.

Varicose veins are common in females but onset of the disease is earlier in males. The incidence is about 20 - 25% of the adult female population and 10 - 15% of men in western countries[1].

Primary varicose veins:

They occur as result of congenital weakness in the vessel wall. It can also be due to muscular weakness or due to congenital absence of valves. Primary varicosity can also be familial. These factors, in addition to prolonged standing, help in the development of the varicose veins. Varicosity is the penalty for verticality against gravity.

Klippel-Trenaunay syndrome is a congenital venous abnormality wherein superficial and deep veins do not have any valves. It is also called as "valveless syndrome".

Secondary varicose veins:

Women are more prone for varicose veins because of the following reasons:

1. Pregnancy and pelvic tumours.
2. Pills (oral contraceptive pills) alter the viscosity of blood.
3. Progesterone dilates vessel wall.
4. Congenital arterio-venous fistula increases blood flow and increases venous pressure.
5. Deep vein thrombosis can result in destruction of valves resulting in varicose veins.

Spider veins are similar to varicose veins, but they are smaller. They are often red or blue and are closer to the surface of the skin than varicose veins. They can look like tree branches and spider webs with their short jagged lines. Spider veins can be found on the legs and face. They can cover either a very small or very large area of skin. Chronic venous insufficiency may result in feeling of heaviness, tendency for swelling, leg pain, and leg ulcer.

The prevalence of varicose veins in different countries is shown below:

Country	Prevalence in males (%)	Prevalence in females (%)
Germany (Maori tribe)	36.3	47.4
UK	10 - 15	20 - 25
Portugal	20.7	40.8
Western Jerusalem	10	20
USA	40 - 45	50 - 55

Patients and methods

All patients of varicose veins of lower limb who had attended the OPD of cardiovascular and thoracic surgery department, RIMS, Imphal, from 2001 to 2010 were included in this study. A total of 432 patients had attended the OPD. All the patients were examined clinically. Necessary tests and investigations were done. Diagnosis was further confirmed with Duplex ultrasonography.

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Table I: Varicose vein patients at cardiovascular and thoracic surgery OPD, RIMS, Imphal.

S. no.	Year	No. of cases	Sex		Side		
			Male	Female	Right	Left	Bilateral
1	2001	18	13	5	12	4	2
2	2002	16	9	7	11	5	0
3	2003	17	13	4	10	6	1
4	2004	52	37	15	23	23	6
5	2005	57	52	5	32	24	1
6	2006	46	31	15	14	27	5
7	2007	42	36	6	24	16	2
8	2008	46	34	12	14	23	9
9	2009	65	36	29	25	31	9
10	2010	73	45	28	28	24	21
	Total	**432**	**306**	**126**	**193**	**183**	**56**

A total of eighty patients were operated during this period (2001 to 2010).

Table II: Operated cases of varicose veins in the department of cardiovascular and thoracic surgery, RIMS, Imphal.

S. no.	Year	No. of	Sex		Side		
		operated cases	Male	Female	Right	Left	Bilateral
1	2001	4	1	3	3	0	1
2	2002	5	3	2	3	2	0
3	2003	6	4	2	3	3	0
4	2004	6	6	0	4	2	0
5	2005	8	7	1	3	4	1
6	2006	13	8	5	3	8	2
7	2007	6	5	1	4	2	0
8	2008	7	2	5	2	4	1
9	2009	14	9	5	2	7	5
10	2010	11	8	3	2	3	6
	Total	**80**	**53**	**27**	**29**	**35**	**16**

Though different types of treatment are available, SFJ (sapheno-femoral junction) ligation and LSV (long saphenous vein) stripping are the commonest surgical procedures in this study.

Table III: Operation performed in the department of cardiovascular and thoracic surgery, RIMS, Imphal.

S. no.	Operation performed	No. of cases
1	SFJ ligation only	0
2	SFJ ligation and LSV stripping	45
3	SFJ ligation + LSV stripping + phlebectomy of residual varicosities	25
4	SFJ ligation + LSV stripping + SSV stripping	10

The incidence is more in males, consisting 70.9%; and in females 29.1%. Right side is affected more consisting 44.9% and left only 42.3%. Bilateral limbs are affected in 13%. In the operated cases, males comprised of 66.2% and females 33.6%.

In the post-operative period, any complications like haemorrhage, haematoma, or infection were noted. A male patient who also had HIV infection, had haematoma in the thigh; and another female patient had paraesthesia on the lower limb in the post-operative period. They were managed conservatively.

Results

A total of 432 cases of varicose veins of the lower limb

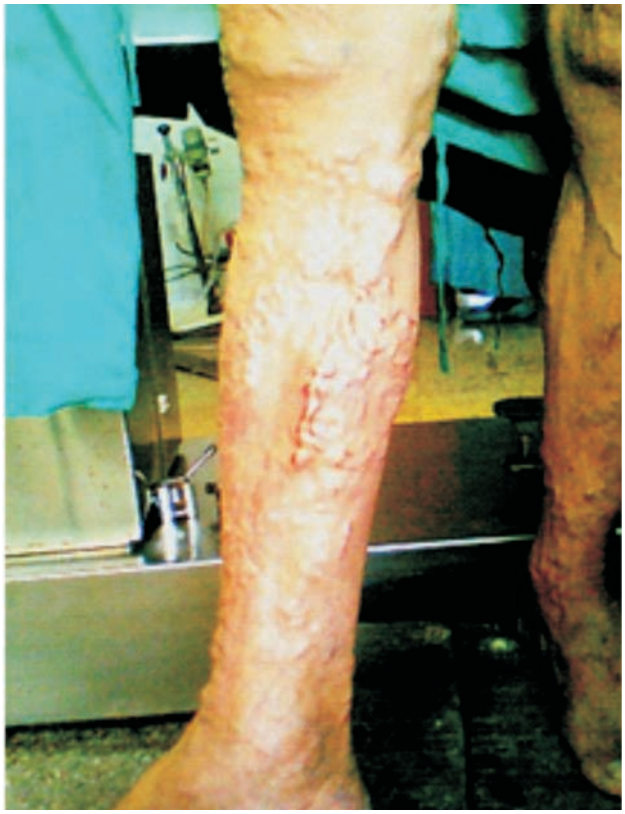

Fig 1: *Varicose veins on antero-medial aspect of the right leg.*

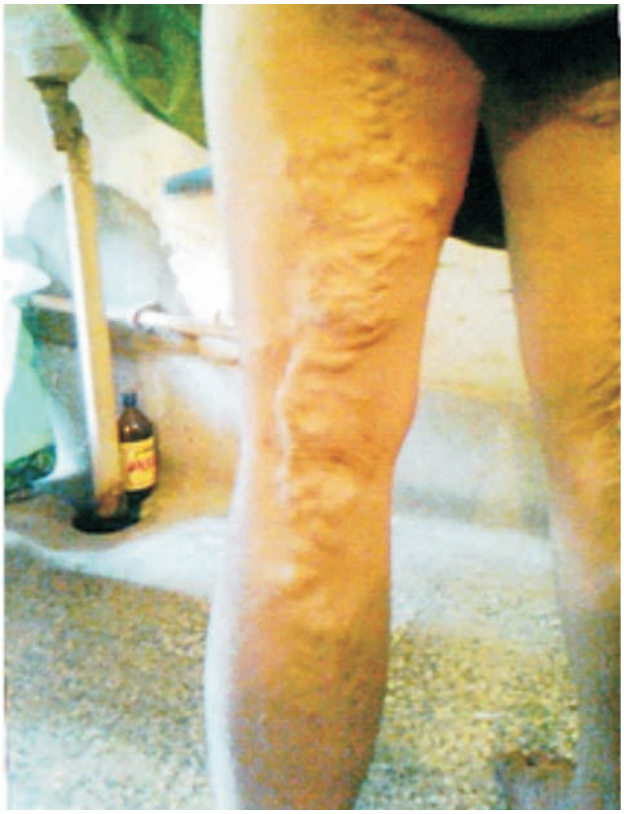

Fig 2: *Varicose veins on the back of the left thigh.*

had attended in the out-patient department of cardiovascular and thoracic surgery, RIMS, Imphal; and 80 cases were operated from 2001 to 2010.

The post-operative complications like pain, wound abscess, aching, itching were minimal. One patient had paraesthesia and another had haematoma on the operated site. Venous assessment was repeated in all patients 3 months after surgery.

Discussion

Disease of the venous system is a major problem affecting western societies resulting in considerable morbidity in the population and cost to the health services. Also, in many countries, varicose veins are probably the commonest disorder presenting to the general surgeons[2].

The surgical treatment of varicose veins can be achieved in different ways like:-

i) Trendelenburg's operation + stripping + phlebectomies of remaining varicosities.

ii) Trendenlenberg's operation + stripping + subfascial ligation.

iii) Sub-fascial ligation.

iv) Endovascular laser treatment (EVLT).

v) Transilluminated powered phlebectomy (TIPP).

vi) Radio-frequency ablation (RFA) waves to close the varicose veins.

vii) Catheter-assisted ablation of veins.

We had not done SFJ ligation only because recurrences of varicose veins are very high. Majority of the patients had SFJ ligation and LSV stripping. But it is reported that Trendenlenberg's operation with subfascial ligation has given good results[3].

Glass has recently proposed that recurrence of varicose veins may be the result of 'neovascularisation' of the ligated long saphenous vein (LSV)[4]. This may be true when the LSV is left in situ, but it does not explain the incidence of reflux where the LSV is stripped. Stripping the LSV to the upper calf does not result in a higher incidence of injury to the saphenous nerve[5]. In the post-operative period, LSV reflux is more completely abolished by combining LSV stripping with SFJ ligation. SFJ ligation is the commonest cause of recurrence[6].

The principal outcome measures were abolition of reflux in the treated segment of the great saphenous vein (technical success) and improvement in disease-specific quality of life 3 months after treatment (clinical success).

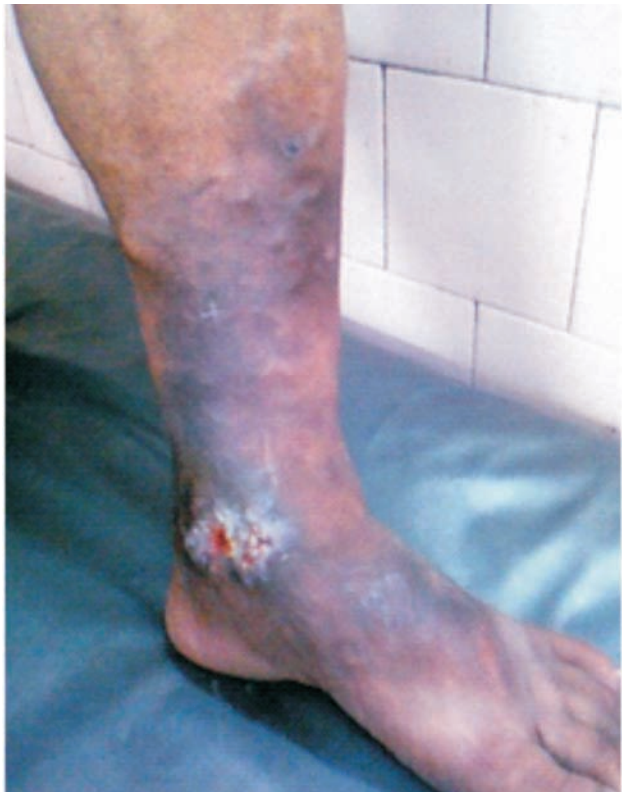

Fig 3: *Complication (venous ulcer) of varicose vein.*

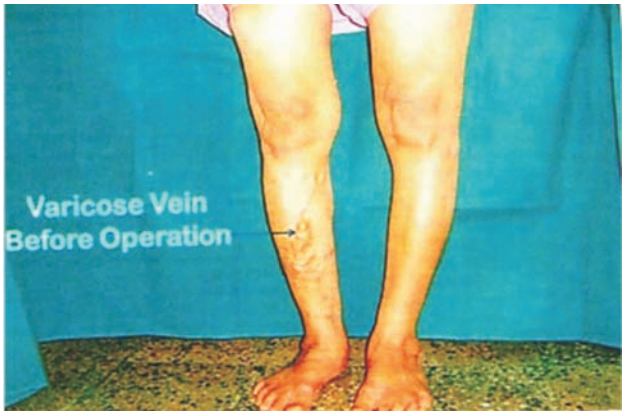

Fig 4: *Varicose vein on the right leg before operation.*

From the data available, it appears that EVLA (endovascular laser ablation) and surgery were equally effective in abolishing SFJ and GSV reflux. The improvement in disease -specific quality of life and cosmesis was similar for all treatments, as was patients' satisfaction. The magnitude of symptom improvement was similar to that reported by other studies and was accompanied by an improvement in Venous Clinical Severity Score (VCSS)[7,8].

Patients undergoing a bilateral stripping operation did not differ from those undergoing unilateral operation.

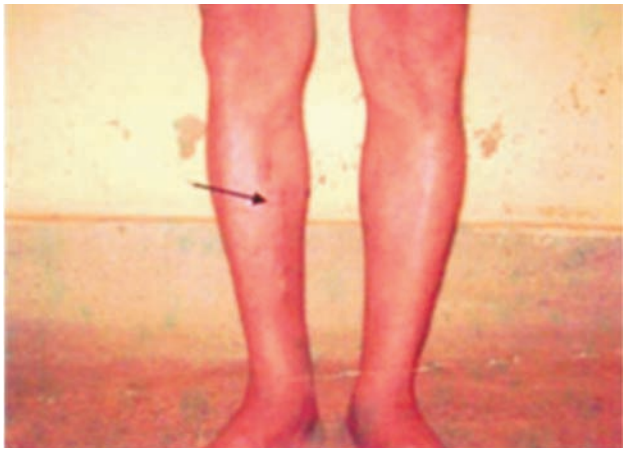

Fig 5: *Varicose vein on the right leg after operation.*

Therefore we recommend bilateral operation to some patients when indicated. Although some recurrence of varicose veins is frequent at 10-years after operation, surgery provides long-term relief of symptoms in the great majority of patients[9].

Conclusion

Varicose veins is a chronic morbid condition. Though newer techniques like Endovenous Laser Treatment (EVLT), Transilluminated Powered Phlebectomy, and Radio-Frequency Ablation (RFA) are available, surgical treatment by stripping of the long and short saphenous veins with the ligation of SFJ is an established effective treatment of varicose veins in our centre. Patients were followed-up regularly in the out-patient department for detection of any recurrent or residual varicosities.

The Framingham Study of Boston University suggests that increased physical activity and weight control may help prevent varicose veins among adults at high risk and reduce the overall risk of atherosclerotic cardiovascular disease as well[10].

Acknowledgement

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"Dream as if you will live forever.
Live as if you will die today."

– James Dean.

ORIGINAL ARTICLE

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Pattern of prevalence of risk factors for non-communicable diseases in the geriatric population of district Dehradun

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Abstract

Background: Globally, non-communicable diseases are the major cause of morbidity and mortality. According to the WHO Report 2004, they account for almost 60% of deaths and 47% of the global burden of disease. In India, estimated deaths due to NCDs were double than those from communicable diseases. A progressive rise in the disease pattern of NCD foretells a serious public health issue.

Objective: To compare risk factors for non-communicable diseases in the geriatric population of district Dehradun.

Methods: This cross-sectional study was conducted in rural (Doiwala block) and urban (Dalanwala) areas of district Dehradun, Uttarakhand. 244 elderly persons of age 60 years and above were interviewed on a predesigned pretested questionnaire by house to house visits in the study area.

Results: 159 (64.7%) out of 244 geriatric study subjects were 60 - 70 years of age. Prevalence of malnutrition was higher (35.5%) in the rural area, whereas over-nutrition was a major problem in the urban area, i.e., overweight (31.1%) and obese (13.9%). Overall, 29.5% study subjects had BMI of 25 & above.

High risk group as per Waist–Hip ratio were more in the rural (33%) geriatric population as compared to the urban (21.3%) population. Anaemia was more in the rural geriatric population (41.9%). Pre-hypertensives (29.5%) and hypertensive (44.3%) were more in urban area. 15.2% were having total cholesterol level above the desirable limits, which was more pronounced in urban area (18.1%). Prevalence of non-communicable diseases was on the higher side in the urban area: hypertension (59.3%), arthritis (32.0%), cataract (28.5%), diabetes (25.2%), and heart diseases (22%).

Conclusions: Prevalence of high-risk factors for chronic diseases (non-communicable diseases) like hypertension, dyslipidaemia, and diabetes mellitus is quite high amongst the elderly population, especially amongst urban counterparts.

Key words: Elderly, non-communicable disease, high risk factors.

Background

Non-communicable diseases (NCDs) are becoming a leading cause of morbidity and mortality in India. The high prevalence of major risk factors, viz., tobacco and alcohol consumption, inappropriate diet, physical inactivity, high blood pressure, high blood glucose and dyslipidaemias are driving the epidemic of NCDs[1]. About 53% of deaths are due to diseases such as cancers, cardiovascular diseases diabetes and chronic respiratory diseases[2]. This puts a substantial burden on the existing health care system and is projected to increase in future. The economic implications of this increased burden on our health system cannot be debated.

About 80% of the global burden of disease is shared by low- and middle-income countries out of which 75% of the diseases occur in individuals more than 60 years of age[3]. Cardiovascular diseases, stroke, and peripheral vascular diseases cause more deaths than HIV, malaria, and tuberculosis[4], while they continue to draw the attention of international funding agencies which direct greater research in these areas.

The WHO has developed a STEP-wise approach for surveillance of NCDs where information at various levels is collected with standardised tools and protocols. This ensures reliable information which is comparable over time and across regions[5]. It involves various steps. To begin with, information is collected by interviews for usage of tobacco and alcohol and dietary and physical activity pattern. Later, blood pressure and anthropometric measurements followed by blood collection for diabetes and cholesterol are done using standardised instruments.

Unlike many developed nations, there is no well-structured geriatric health service cell in India. India is in a phase of demographic transition where 60 plus population is projected to quadruple by 2050[6]. This calls for an urgent action to address the needs of the rural as well as urban elderly population of India especially with regard to NCDs. With this purpose in mind, a cross-sectional study was conducted in rural as well as urban area of Dehradun district. The objective of the study was

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to compare the prevalence of risk factors of NCDs in rural and urban elderly population of Uttarakhand.

Methodology

Initially a cross-sectional study was conducted as part of community based health registry project of Doiwala block, Dehradun (Uttarakhand) to assess the health status of elderly population in a rural setup. There are 168 villages in Doiwala block, out of which one village, Dharmuchak was randomly selected. The study was conducted in March – April, 2010. This study attempted to include all the households and residents of the village who were above 60 years of age. There were 122 individuals aged $\geq$ 60 years, this also corresponds to 8 % of geriatric population, being the national average. Sample size can also be calculated by following method: $n = 4pq/l^2$.

Here p is the approximate percentage of geriatric population in a defined community, i.e., 8% with approx. sample size = 120.

The survey used the validated WHO STEP-wise approach to surveillance questionnaire[7] and included information on tobacco use, diet, physical activity (ADL), weight and blood pressure. The questionnaire was pretested and modified to fit Indian conditions after pilot testing on a subpopulation in both the areas. Data were also collected on the age, sex, level of education, occupation, and health status and risk factors for emerging diseases of each participant. Data was collected using mentioned tool questionnaire through interview method by trained investigators.

Biological and anthropological risk factors were assessed by measuring the height, weight, and blood pressure of each participant. The BMI (kg/m^2) was calculated from the height and weight of each participant. Blood pressure was recorded in the right arm, in a sitting position, to the nearest 1 mmHg, using a digital sphygmomanometer (OMRON-MX2 with adult size cuff). Two readings were taken 5 minutes apart and the mean of the two was taken as the blood pressure.

The results obtained in the rural study motivated the investigators to plan a similar study in the urban area as an extension (Phase II) of this study.

In Phase II, a similar study was planned to compare rural geriatric population belonging mostly to illiterate lower socio-economic group with urban population mostly belonging to literate and upper socio-economic status.

This comparative study was conducted in an urban (Dalanwala) area of district Dehradun of Uttarakhand, during April - June, 2010. A similar comparative sample of 122 individuals aged $\geq$ 60 years were registered in the study area by systematic random sampling method.

The survey population was pre-informed about the objectives of the survey. After taking informed consent, a pre-designed, pre-tested, closed-ended questionnaire was used for conducting this study, through interview method on individual basis by trained investigators. This study had attempted to include all the households and residents of the study areas who were above 60 years of age. Only those individuals willing to participate in the study were selected till the requisite sample size was achieved.

Further, a blood sample was also collected from the volunteered participants and some baseline lab investigations were also done, i.e., haemoglobin, blood sugar, serum cholesterol, as in rural study.

The collected information was entered in the computer and analyzed by using SPSS software. Thus proportions and Chi-square test were calculated ($p < 0.05$). The data between the two geriatric groups, i.e., Dehradun – rural (Dharmuchak) and Dehradun – urban (Dalanwala) was compared to assess the health and socio-economic indicators.

Results

122 geriatric persons were surveyed in a village of population 1,348 in a rural area, amounting to 9.05% elderly population, while a similar sample, i.e., 122 was taken from an urban area. Out of the total 244 study subjects, 81 (33.1%) were females and 163 (66.8%) were males. Most of them belonged to 60 - 70 years of age, i.e., 159 (64.7%), while 18 (7.3%) were more than 80 Years of age. Mean Age of the geriatric population was 68.00 ± 2 X 7.52 SD.

Prevalence of malnutrition was higher (35.5%) in rural area as compared to urban (3.3%). Whereas over-nutrition was a major problem in urban area, i.e., overweight (31.1%) and obese (13.9%). Overall 29.5% (both areas combined) study subjects were having BMI of 25 and above, high risk group.

High risk (male:1.0+, Female: 0.85+) group as per Waist–Hip ratio were more in rural(33%) geriatric population as compared to urban (21.3%). Combined high risk group were 26.7%. Moderate risk as per Waist–Hip ratio in the geriatric study group was 22.8%.

Anaemia was more in the rural geriatric population (41.9%) as compared to urban area (13.8%), with overall prevalence of 23.6%. This difference was found to be statistically significant ($p < 0.000$).

Pre-hypertensives (29.5%) and hypertensives (44.3%) were more in urban area as compared to 24.1% and 30.5%

in rural area. 15.2 % were having total cholesterol level above desirable limits, which is more pronounced in urban area (18.1%) as compared to rural (10.3%). Diabetics were more in Urban (12.1%) area, while overall blood glucose level in geriatric study group was 8.7%.

Table I: High risk analysis – nutritional status indicators in geriatric population.

Nutritional status indicator	Rural	Urban	Total	ü2
Body mass index (kg/m2)				
Normal (18.50-24.99 kg/m2)	52 (48.6%)	63 (51.6%)	115 (50.3%)	
Underweight (< 18.50 kg/m2)	38 (35.5%)	4 (3.3%)	42 (18.3%)	
Overweight (25.00-29.99kg/m2)	11 (10.3%)	38 (31.1%)	49 (21.4%)	.000
Obese (≥ 30.00kg/m2)	6 (5.6%)	17 (13.9%)	23 (10.0%)	
Total	107	122	229	
Waist-hip ratio				
Low risk (Male 0.95 or below, Female - 0.80 or below)	55 (51.9%)	60 (49.2%)	115 (50.5%)	
Moderate risk (Male - 0.96 to 1.0, Female - 0.81 to 0.85)	16 (15.1%)	36 (29.5%)	52 (22.8%)	.000
High risk (Male - 1.0 +, Female - 0.85 +)	35 (33.0%)	26 (21.3%)	61 (26.7%)	
Total	106	122	228	
Anaemic status (Haemoglobin level gm/dl)				
Normal	36 (58.1%)	100 (67.1%)	136 (76.4%)	
Anaemic (Male < 13 gm/dl, Female < 12 gm/dl)	26 (41.9%)	16 (13.8%)	42 (23.6%)	.000
Total	62	116	178	

Table II: Prevalence of high risk factors.

High risk factors for non-communicable disease				
Indicator	**Rural (%)**	**Urban (%)**	**Total (%)**	**ü2**
Blood pressure (mm of Hg)				.000
Normotensive (< 120)	49 (45.4%)	32 (26.2%)	81 (35.2%)	
Pre-hypertensive (120-139)	26 (24.1)	36 (29.5%)	62 (26.9%)	
Hypertensive stage I	22 (20.1%)	29 (23.8%)	51 (22.2%)	
Hypertensive stage II	11 (10.2%)	25 (20.5%)	36 (15.6%)	
Total	108	122	230	
Total cholesterol level				.000
Desirable (< 200 mg/dl)	61 (89.7%)	95 (82.0%)	156 (84.8%)	
Borderline high (200-239 mg/dl)	4 (5.9%)	17 (14.6%)	21 (11.4%)	
High (> 240 mg/dl).	3 (4.4%)	4 (3.4%)	7 (3.8%)	
Total	68	116	184	
Blood Glucose level				.000
Normal	63 (92.7%)	89 (76.7%)	152 (82.6%)	
Pre-diabetes (>140 mg/dl)	3 (4.4%)	13 (11.2%)	16 (8.7%)	
Diabetes (> 200 mg/dl)	2 (2.9%)	14 (12.1%)	16 (8.7%)	
Total	68	116	184	

14 persons refused blood pressure monitoring in rural area; 54 persons in rural, and 6 in urban area refused to give blood sample.

Prevalence of non-communicable disease was on the higher side in urban area specially hypertension (59.3%), arthritis (32.0%), cataract (28.5%), diabetes (25.2%), and heart diseases (22%). Overall, hypertension (34.7%) followed by arthritis (17.6%), diabetes (15.5%), cataract (14.7%), heart disease (13.5%), and BPH (11.0%) were common non-communicable diseases observed, while asthma (6.1%), stroke (2.9%), COPD (2.4%), cancer, urolithiasis, piles, varicose veins, and deafness were less common.

93.5% of urban geriatric population have ever had their blood pressure measured by the physician in comparison to 48.4% in rural area ($p < 0.000$); while 77.2% of urban geriatric population have had their blood sugar measured by a physician in comparison to 23% in rural area ($p < 0.000$)

Discussion

Most of the study subjects belonged to 60 - 70 years of age, i.e., 159 (64.7%) similar to a study by Chandwani *et al*[8] (66.2%), in contrast to study done by Bhatt *et al*[9] (72.5%), Lena *et al*[10] (72.3%), and Gurav, Kartikeyan[11] (78.2%) were in this age group, while comparative 7.89% were more than 80 years of age as in the present study (7.3%) in contrast to 9% by Chandwani *et al*[8] and 3.48% by Gurav, Kartikeyan[11]. Mean age of the geriatric population was 68.00 ± 2 x 7.52 SD.

Prevalence of malnutrition was more in rural (35.5%) area as compared to urban (3.3%) (combined: 18.3%), while Bhatia *et al*[12] reported 14.36 % underweight in the geriatric age group in Chandigarh. In the present study, over-nutrition, i.e., overweight (31.1%) and obese (13.9%) was more in the urban geriatric group as compared to the geriatric study group in Chandigarh 25.4% (overweight) and 7.7% (obesity). Overall, about 29.5% study group was having BMI of 25 and above (high risk group) in contrast to Bhatia *et al*[12] finding of 62.5 %.

Though moderate risk group (29.5%) as per Waist–Hip ratio was higher in urban area, high risk group was more in rural (33%) geriatric population; combined high risk group were 26.7%. About half (49.5%) of the geriatric population belonged to the moderate-to-high risk category.

Pre-hypertensives (29.5%) and hypertensives (44.3%) were more in urban area as compared to 24.1% and 30.5% in rural area. While in the study by Datta[13] and Lena *et al* at Udupi[10], 59.1% geriatrics were hypertensive. This is much higher than 16.34% as described by Gurav, Kartikeyan[11] and even higher than 37.5% found by Khokkar *et al*[14]. However, our finding was corroborative with 48% by Prakash *et al*[15]. This finding may be due to the beginning of stressful life and sedentary lifestyle in the gradually expanding capital city of Uttarakhand.

Table III: Prevalence of non-communicable diseases.

Place	Heart disease	Stroke	Arthritis	Hypertension	Diabetes	Asthma	COPD	Cataract	BPH
Rural	6 (4.9)	0	7 (5.7)	14 (9.8)	7 (5.7)	1 (0.8)	1 (0.8)	1 (.8)	0
Urban	27 (22.0)	7 (5.7)	39 (32.0)	73 (59.3)	31 (25.2)	14 (11.5)	5 (4.0)	35 (28.5)	27 (22.0)
Total	33 (13.5)	7 (2.9)	43 (17.6)	87 (34.7)	38 (15.5)	15 (6.1)	6 (2.4)	36 (14.7)	27 (11.0)
	.000	.008	.000	.000	.000	.000	.049	.000	.000

15.2 % were having total cholesterol level above desirable limits, which is more pronounced in urban area (18.1%) as compared to rural (10.3%). Blood glucose level > 200 mg/dl (diabetes) was more in urban (12.1%) area, while overall higher blood glucose level in geriatric study group was 8.7%, though self-reported diabetics were 25% in urban area as compared to 5.7% in rural area with combined prevalence of 15.5%. Bhatia *et al*[12] reported prevalence of 11.9% for diabetes mellitus in aged persons. Both these risk factors of NCDs are on the higher side in the urban population due to rapidly changing lifestyle of geriatric people, as urbanisation activities and stressful life are evident in Dehradun.

Overall hypertension (34.7%) followed by arthritis (17.6%), diabetes (15.5%), cataract (14.7%), heart disease (13.5%) and BPH (11.0%) were common non-communicable disease observed, while asthma (6.1%), stroke (2.9%), COPD (2.4%), cancer, urolithiasis, piles, varicose veins, and deafness were less common morbidities. While Lena *et al*[10] reported higher prevalence of hypertension (59.1%), osteoarthritis (41.3%) and diabetes (10.3%).

Conclusion

The present study has highlighted a high prevalence of morbidity among the urban geriatric study group and has identified more common existing high risk factors like obesity, abnormal waist-hip ratio, high cholesterol and blood glucose level among rural and urban geriatric study group. Medical problems like hypertension, arthritis, cataract, and diabetes mellitus were common among this age group, and with progressive increase in the number of elderly population, this burden will increase especially in rural areas which were earlier considered epicentre for communicable disease alone. There is an urgent need to develop geriatric health care services by providing training to health care providers to manage the commonly existing health problems among the elderly.

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ORIGINAL ARTICLE

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Spectrum of opportunistic infections among HIV/AIDS patients of Tripura

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Abstract

Introduction: The staggering worldwide evolution of HIV pandemicity is a major concern today as it causes a greater loss of productivity than any other diseases. HIV infection leads to profound immune deficiency and patients become highly susceptible to opportunistic infections. HIV epidemic in India is heterogeneous in nature, both in terms of routes of transmission as well as geographical spread.

Aims of the study: Determination of the prevalence of opportunistic infection among HIV seropositive patients and their relation to CD4 cell count and to focus on the routes of transmission in the State of Tripura in north-east India.

Materials and method: This is single-centre prospective study including all the patients attending Anandalok Community Care Centre during the period of 1st October 2008 to 30th September 2011.

Result: Among 281 (n) patients 73% were male and 27% were female. Mean age of the study group was 33.47 (SD 9.577) years. Among the opportunistic infections (OIs) prevalence of TB was 17.1% and uncomplicated respiratory tract infection, candidiasis, chronic diarrhoea, skin fungal infection, urinary tract infection, sexually transmitted infection were respectively 22.1%, 14.2%, 5.3%, 3.2%, 2.8%, and 2.1%. The most common mode of transmission was heterosexual transmission (89.08% in males and 94.28% in females).

Conclusion: The frequency of OIs among the HIV/AIDS patients of Tripura is less but it has got a similar linear relationship with CD4 cell count. This study is the first ever reported data on OIs among HIV/AIDS patients from Tripura, and this will serve as a matrix for future evaluation.

Key words: HIV - human immunodeficiency virus, AIDS - acquired immunodeficiency syndrome, CCC - community care centre, PLHA - people living with HIV/AIDS, OI - opportunistic infection, PTB - pulmonary tuberculosis , EPTB - extra-pulmonary tuberculosis.

Introduction

Humankind has been besieged throughout its evolution by microorganisms that pose a continual challenge to the survival of the species[1]. The staggering worldwide evolution of HIV pandemicity is a major concern today as it causes a greater loss of productivity than any other disease, and is likely to push an additional 6 million households into poverty by 2015 unless national responses are strengthened (commission on AIDS, 2008)[2]. According to the UNDP, HIV has inflicted the "single greatest reversal in human development" in modern history (UNDP, 2005). Globally, there were an estimated 33 million (30 - 36 million) people living with HIV in 2007. According to UNAIDS and WHO estimates, 4.9 million (3.7 - 6.7 million) people were living with HIV in Asia in 2007, and approximately 300,000 people died from AIDS-related illness in 2007. Young people aged 15 to 24 account for an estimated 45% of new HIV infections worldwide[3]. The first case of HIV/AIDS in India was detected in 1986 in the state of Tamil Nadu, and ever since, the spread of HIV/AIDS across the nation has been relentless. There are 2.39 million (1.93 - 3.04 million) people living with HIV/AIDS in India with an estimated adult prevalence of 0.31% (0.25% - 0.39%). Out of the estimated number of PLHA, 39% are females and 3.5% are children[4].

HIV infection leads to profound immunodeficiency resulting primarily from progressive quantitative and qualitative deficiencies of the subset of T-lymphocytes referred to as helper T cells (CD4)[5]. In the untreated patient, the CD4+ T cells count falls rapidly and the patient becomes highly susceptible to opportunistic infections like tuberculosis, candidiasis, *Pneumocystis jiroveci* pneumonia (PCP), cryptococcal meningitis, parasitic diarrhoea, hepatitis, herpes zoster, UTI, etc. Death in HIV infection is mostly due to opportunistic infections. Pulmonary disease is one of the most frequent complications of HIV infection and worldwide approximately 1/3rd of all AIDS-related deaths are associated with tuberculosis[5]. But the prevalence is variable from country to country and in different regions. Merchant *et al* from Mumbai reported that among opportunistic infections, pulmonary and extra-pulmonary tuberculosis was 24.47% and skin lesions, chronic diarrhoea, oral candidiasis, recurrent LRTI, pneumocystis pneumonia were 22.10%, 15.08%, 14.73%, 8.42%, and

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3.88% respectively[6]. In another study, Pol from Karnataka revealed that 38.03% was tuberculosis, recurrent diarrhoea (30.99%), oral candidiasis (21.13%), and recurrent bacterial pneumonia (12.68%)[7]. Sharma *et al* reported a higher prevalence of tuberculosis (71.1%) among hospitalised HIV patients in a tertiary care hospital at Delhi[8].

The HIV epidemic in India is heterogeneous in nature, both in terms of routes of transmission as well as geographic spread. HIV infection is predominantly sexually transmitted and the most common mode of infection, particularly in the developing countries, is heterosexual transmission, without exception to India. But prevalence among IDUs (7.2%) in India is on the increase, whereas low prevalence is seen among antenatal clinic attendees (population adjusted 0.48%)[4].

The widespread use of effective chemoprophylaxis for opportunistic infections and the use of HAART have resulted in a delay in the onset of AIDS, longer survival, and a change in the pattern of opportunistic infection in the developed world. The present study was undertaken to estimate the specific opportunistic infections, their relation with CD4 lymphocyte counts, and to focus on the routes of transmission in Tripura State.

Aims of the study

1. Determination of the prevalence of opportunistic infections among HIV seropositive patients and their relation to CD4 cell count.
2. Analysis of the routes of transmission of HIV in Tripura.

Material and methods

This is a single-centre prospective study which includes all patients attending the Community Care Centre (CCC) 'Anandalok' for hospitalisation and subsequent regular follow-up in an OPD-based setting during the period from 1st October 2008 to 30th September 2011. These patients were already diagnosed HIV-positive from the lab of ICTC. All the patients who were registered in the CCC were included in this study after taking written consent. Every patient once included had a follow-up done at monthly intervals. These patients were thoroughly examined clinically and investigated extensively for diagnosis of opportunistic infections. A specific opportunistic infection was diagnosed on the basis of standard clinical definition and by laboratory procedures[9,10]. Patients were advised to initiate anti-retroviral therapy (ART) when their CD4 cell count was less than 250/µL according to the existing guidelines of NACO at the time of study, and ART drugs were supplied from the ART centre. CD4 cell counts were estimated by FACS count flowcytometer at the interval of 6 months subsequently. Tuberculosis is diagnosed and treated as per RNTCP guidelines. HBV and HCV were confirmed by ELISA, and VDRL was used to diagnose STI. Routine urine examination (pus cells >10/HPF is positive) was done for the confirmation of UTI. For candidial infections, KOH wet mounting was done for fungal hyphae.

All the data was entered by use of a standardised collection form that documented age, sex, mode of HIV transmission, date of HIV detection, presenting symptoms and opportunistic infections, CD4 lymphocyte counts, different blood investigations, and treatment. Data entry, database management, and analysis was done with the use of SPSS 17. Descriptive statistics were used to calculate the frequency, mean, median, mode, and standard deviation.

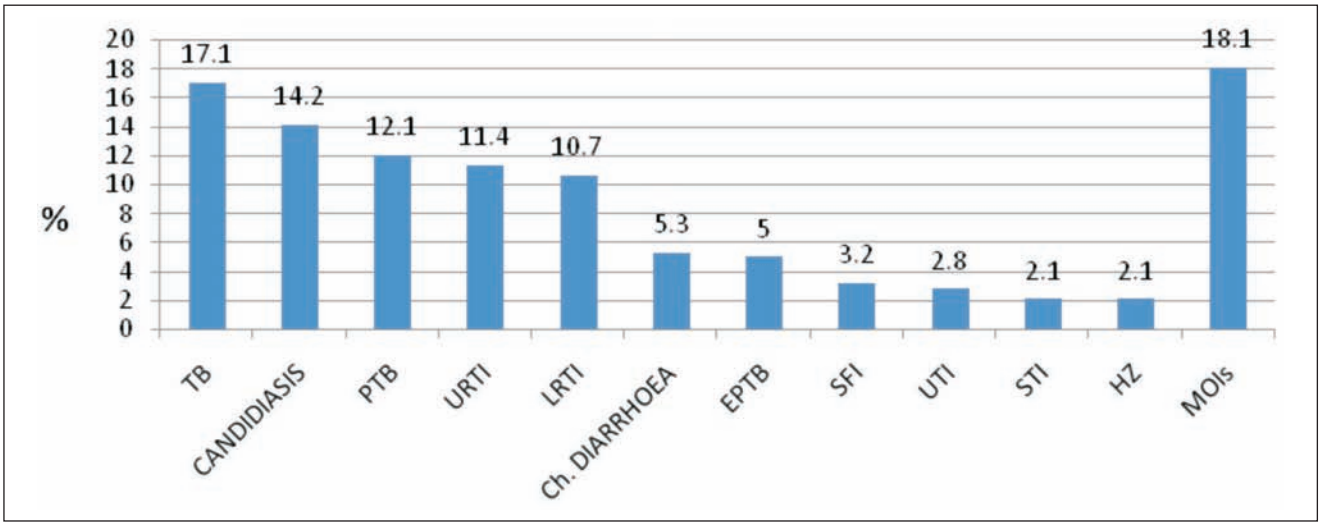
Results

Over a period of three years, 281 (n) patients with HIV/AIDS were admitted to Anandlok Community Care Centre and were included in this study. Mean age of the study group was 33.47(SD 9.577) years, among these patients 73% were male and 27% were female. Mean CD4 cell count of the study group was 267.11 (232.316) cells/µL. Out of these, 186 (66.2%) patients were put on anti-retroviral treatment. The mean CD4 cell count of the patients on anti-retroviral treatment reduced subsequently to 151.47 (104.633) cells/µL.

Among the study population (n = 281), 17.1% were having tuberculosis; out of this, 41.17% were having extra-pulmonary tuberculosis. Among all other opportunistic infections, candidiasis was significant in prevalence, i.e., 14.2%. Uncomplicated respiratory tract infections constituted 22.1%. Other co-infections like chronic diarrhoea, skin fungal infection, urinary tract infection, sexually transmitted infections, and herpes zoster were of low incidence: respectively 5.3%, 3.2%, 2.8%, 2.1%, and 2.1%. Out of all HIV/AIDS patients, 18.1% had multiple opportunistic infections. The prevalence of different opportunistic infections among the PLHA patients are shown in Table I.

The most predominant route of transmission of HIV in Tripura is heterosexual transmission in males (89.08%) and females (94.28%) followed by vertical transmission (3.5% in males and 5.71% in females). Homosexual transmission is 2.29% and 1.72% is due to intravenous drug abuse (IDU).

Table I: Prevalence of different opportunistic infections among the study group.



TB = Tuberculosis; PTB = Pulmonary tuberculosis; EPTB = Extra pulmonary tuberculosis; URTI = Upper respiratory tract infection; UTI = Urinary tract infection; STI = Sexually transmitted infection; SFI = Skin fungal infection; HZ = Herpes zoster; LRTI = Lower respiratory tract infection; MOIs = Multiple opportunistic infections.

Discussion

Community care centres are care and support centres for HIV/AIDS patients. Patients are usually referred from ART centres before initiation of ART to observe drug tolerance and compliance and also for extensive counselling. As the CCCs are having in-patient treatment facilities, almost all symptomatic HIV/AIDS patients are usually referred to CCC for in-patient care. ART Centre at Agartala Government Medical College is very nearby to "Anadalok" CCC, hence almost all patients are referred to our CCC. Hence our patient population represents almost total HIV/AIDS burden of the state of Tripura. During the study period of 3 years we have evaluated 281(n) patients. The average age group of patients were 33.47(SD 9.577) and male to female ratio was 2.7 : 1. On evaluation we have found that 41.6% of our patients were admitted with some or other opportunistic infection. Among OIs TB was most common, i.e., 17.1%, followed by candidiasis 14.2%. Among TB patients, 58.83% were having PTB, and 41.17% were having EPTB. But Sharma *et al* reported a much higher incidence of TB (71.1%) in New Delhi[8], whereas Kumarasamy *et al* from southern India reported 49.3% of HIV infected patients had PTB in respect to 11% EPTB in a retrospective analysis of 594 HIV-positive patients.[12] In another study, Patel from Ahmedabad revealed that candidiasis was the commonest isolate (32.67%), followed by TB (22.71%)[13]. In this study we have found that most of the TB infections were present among the patients having CD4 cell counts below 350/µL and mean CD4 cell count were 127.68 (95.326)/µL and 170.71 (109.412)/µL in the pulmonary and extra-pulmonary TB infected patients respectively.

Among other OIs, uncomplicated respiratory tract infection (22.1%) was common in Tripura. Whereas chronic diarrhoea (5.3%), skin fungal infection (3.2%), UTI (2.8%), STI (2.1%) were lower in prevalence than other parts of the country. Saha *et al* reported from Kolkata that common opportunistic infection were oral candidiasis (53.43%), chronic diarrhoea (47.05%), and TB (35.29%)[14].

It has been observed that 41.6% of the HIV infected patients had any one of the opportunistic infection and a lower baseline CD4 cell count 190.91 (194.882)/µL in comparison to 321.48 (241.951)/µL in patients without any opportunistic infections. Uncomplicated respiratory tract infections, urinary tract infection, STI, candidiasis, chronic diarrhoea were the more prevalent opportunistic infections when CD4 cell counts fells below 350/µL.

Table II: Occurrence of OIs in relation to CD4 cell count.

Opportunistic infections (OIs)	CD4 ≤ 200 cells/µL	CD4 > 200 - 350 cells/µL	CD4 > 350 cells/µL
PTB	27 (19.7%)	6 (8.1%)	1 (1.4%)
EPTB	9 (6.6%)	4 (5.4%)	1 (1.4%)
LRTI	23 (16.8%)	6 (8.1%)	1 (1.4%)
URTI	23 (16.8%)	4 (5.4%)	5 (7.1%)
UTI	6 (4.4%)	1 (1.4%)	1 (1.4%)
STI	4 (2.9%)	1 (1.4%)	1 (1.4%)
Candidiasis	30 (21.9%)	7 (9.5%)	3 (4.3%)
Chronic diarrhoea	14 (10.2%)	1 (1.4%)	–
SFI	6 (4.4%)	3 (4.1%)	–
HZ	4 (2.9%)	2 (2.7%)	–
MOIs	37 (27%)	10 (13.5%)	4 (5.7%)

HIV is now spreading from high risk behaviour group to general population, and from urban to rural population. From our study we have found that the most common mode of transmission in our state is heterosexual transmission (89.08% in males and 94.28% in females). Homosexual and bisexual transmission is 2.29% and 3.44% only in males. According to the NACO annual report 2010-2011, 87.4% was heterosexual and 1.3% was homosexual transmission[4]. Intravenous drug abuser (IDU) constitute 1.72% of transmission in Tripura which is consistent with other parts of the North-Eastern states of India.

Conclusion

The present study reflects that among the HIV/AIDS patients of Tripura, the frequency of OIs is less but it has a similar linear relationship with CD4 cell count. The cause of less incidence of OIs may be due to inclusion of all admitted HIV/AIDS patients in the study, though all these patients were symptomatic and had reported to the health facility for treatment. The relationship of our HIV positive patients with their nutritional status and BMI could not be evaluated. Further HIV RNA and genotype study may throw some light on the causation of low incidence of opportunistic infection among HIV/AIDS patients of Tripura. But this study once again proves that the spectrum of opportunistic infections among various patient groups varies significantly. This study is the first ever reported data on OIs among HIV/AIDS patients from Tripura. This will serve as a matrix for future evaluation.

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"A flood of troubles will vanish the moment the mind of a wise man collects itself to face them."

– Tiruvalluvar, *Tirukural*.

ORIGINAL ARTICLE

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Clinical profile of coeliac disease in Himachal Pradesh

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Abstract

***Background:** Coeliac disease (CD) is a common problem which exists in almost all parts of the world, but is underdiagnosed. It is considered that this disease is uncommon in India. The present study was conducted to know the clinical profile of coeliac disease in the state of Himachal Pradesh (HP) in the northern part of India.*

***Methods:** The study was conducted at the Indira Gandhi Medical College and Hospital, Shimla, Himachal Pradesh between August 2009 and August 2011. Two hundred patients presenting with anaemia, chronic diarrhoea, nonspecific abdominal pain, and growth retardation were evaluated for the presence of CD. Twenty-five consecutive patients who fulfilled the diagnostic criteria for CD were included in the study. Along with detailed examination, UGI endoscopy was done in all patients. All patients with coeliac disease were managed with gluten-free diet and follow-up was done for one year.*

***Results:** Out of twenty-five patients, 17 (68%) were female, 8 (32%) were male, and the mean age of patients was 31.3 years. At presentation, 20 (80%) patients were anaemic, diarrhoea was seen in 16 (64%), abdominal distension in 10 (40%), pain abdomen in 8 (36%), and oedema in 1 (4%) patient. The mean serum anti tTG was 87.5 IU/ml. Two patients had chronic liver disease, one patient had autoimmune hepatitis diagnosed after exclusion of common causes and liver biopsy, one patient had hypothyroidism, and one patient had type-I DM.On follow-up, all patients became asymptomatic and the mean haemoglobin was 12 gm%, mean weight 48.3 kg; and mean elevation in haemoglobin was 3.8; and mean weight gain was 7.4 kg within 6 months.*

***Conclusion:** This is the first study from Himachal Pradesh (India) on coeliac disease which revealed that it is not a rare disease. Most of the patients were diagnosed at a later stage – maybe due to late presentation or lack of awareness of the symptomatology of CD among the physicians. Though coeliac disease presents with multiple symptoms, anaemia and diarrhoea are the common presenting symptoms.*

Introduction

Coeliac disease (CD) is an autoimmune gastrointestinal disorder that may occur in genetically susceptible individuals triggered by ingestion of gluten-containing grains such as wheat, rye, and barley. The immunologically based inflammation causes atrophy of the villous structure of the small intestine leading to malabsorption of important nutrients. CD is not uncommon, but it is under-diagnosed. Clinically, CD may present at any age and minor symptoms such as fatigue, dyspepsia, anaemia, or slight weight loss have been found to be increasingly common. The diagnosis is based on demonstration of villous atrophy in duodenal biopsy, and gluten-free diet is the treatment of choice. The data on CD from India is scarce, mostly reported from north India. A community based study done in Ludhiana (Punjab) estimated that coeliac disease prevalence in this city was at least 1 in 310 individuals[1]. However, it is a frequently under-reported condition, and had not yet been reported from Himachal Pradesh (HP). Therefore, this study was conducted with the purpose to know the profile of patients with coeliac disease presenting to a large hospital in Shimla, HP.

Material and methods

This study was conducted at the Department of Gastroenterology, Indira Gandhi Medical College, Shimla, in Himachal Pradesh between August 2009 and August 2011. Two-hundred patients presenting with anaemia, chronic diarrhoea, nonspecific abdominal pain, bloating, and growth retardation were evaluated for the presence of CD. The serum tTG level was done in all patients and UGI endoscopy was done only in patients with high serum tTg level >15 U/ml. Diagnosis of coeliac disease was based on the revised ESPGHAN - (European Society of Pediatric Gastroenterology, Hepatology and Nutrition) criteria, i.e., abnormal villous structure while patient is on gluten diet, and clinical improvement with FGD[2]. Twenty-five consecutive patients who fulfilled the diagnostic criteria for CD were included in the study. The detailed history, physical examination, and investigations which included complete blood count, serum biochemistry, thyroid function tests, and work-up for anaemia were done in all patients. Viral markers, USG abdomen and liver biopsy was done in patients with chronic liver disease and autoimmune hepatitis. Endoscopic findings suggestive of coeliac disease such

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as scalloping and atrophy of folds were noted. The biopsy specimens were taken from the second part of the duodenum, and at least three to six fragments were taken with forceps and sent for histopathological examination. The histological lesion of proximal small intestine was classified according to Marsh classification. All patients with coeliac disease were managed with gluten-free diet and replacement of iron, calcium, and vitamin B12. Follow-up was done for one year, at monthly intervals for the initial 3 months, then every 3-monthly. Improvement in symptoms, elevation in haemoglobin and mean weight gain was noted in every visit.

Results

Out of twenty-five patients, 17 (68%) were female, and 8 (32%) were male. The mean age of patients was 31.3 years which ranged from 9 years to 60 years. Mean body weight was 40.9 kg and its range was 18.60 kg, and mean BMI was 16.33 and the range was 15 - 18.9. Mean delay in diagnosis was 4.5 years, and range was 3 - 10 years from the onset of symptomatology (Table I). At presentation, anaemia was seen in 20 (80%) patients, diarrhoea in 16 (64%), abdominal distension in 10 (40%), pain abdomen in 8 (36%), and oedema in 1 (4%) patient (Table II). Mean haemoglobin was 8.2 gm% and its range was 4 - 10.5 gm%. In all cases, the type of anaemia was microcytic hypochromic. Mean total leukocyte count was 6,700, and mean platelet count was 150,000. In the liver function tests, mean SGOT was 25 and mean SGPT was 22, mean SAP was 90 and total serum bilirubin was 0.2 mg, total mean protein was 6.4 gm and mean albumin was 3.5 gm. Mean serum calcium was 8.2. The mean serum anti-tTG was 87.5 and range was 20 - 295 IU/ml (Table III). Two patients had chronic liver disease, one patient had autoimmune hepatitis diagnosed after exclusion of common causes and liver biopsy, one patient had hypothyroidism and one patient had type-I DM. The UGI endoscopic findings were atrophy of folds in 10 (40%) and scalloping of folds in 12 (48%), and in 3 (12%) patients the endoscopic appearance of duodenal mucosa was normal. Histological examination of D2 biopsies revealed villous atrophy and increased intraepithelial lymphocytes .The histological classification of mucosal lesions of the proximal small intestine was done using Marsh classification. Marsh class type IIIa lesions were present in 8 (32%), Marsh class type IIIb in 6 (24%), and Marsh class type IIIc in 11 (44%) patients. On follow-up, all patients became asymptomatic and mean haemoglobin was 12 gm% and mean weight 48.3 kg, and mean elevation in haemoglobin was 3.8 and mean weight gain was 7.4 kg within 6 months.

Table I: Baseline characteristics of patients at presentation.

Mean age	31.3
Sex – Male	8
– Female	17
Mean weight (kg)	40.9
Mean BMI	16.33
Mean delay in diagnosis	4.5

Table II: Clinical features of patients at presentation.

Symptoms	Cases	Percentage (%)
Pallor/anaemia	20	80
Diarrhoea	16	64
Abdominal distension	10	40
Pain abdomen	8	32
Oedema	2	8
Vomiting	3	12
Constipation	1	4

Table III: Laboratory investigations at diagnosis.

Variables	In patients	In patients (range)
Haemoglobin (g/dl)	8.2	4-14
Total leukocyte/micro-lit	6,700	4,000 - 7,300
Platelets	150,000	350,000
Total protein (gm/dl)	6.4	7.5
Albumin (gm/dl)	3.5	3 - 4.5
Variables	0.2	0.2 - 0.4
SGOT	25	30 - 40
SGPT	22	19 - 30
SAP	90	60 - 130
Mean anti-tTG	87.5	20 - 295

Discussion

In the past, coeliac disease was believed to be a chronic enteropathy, almost exclusively affecting people of European origin. Now, with the availability of simple serological tests (anti-tTG, anti-glidin, and anti-endomysium) have shown that coeliac disease is wide-spread, not only in European countries, but also in the developing countries where the staple diet is wheat[3]. The prevalence of coeliac disease reported from the United States is 1/140 individuals[4]. Gluten intolerance appears to be a widespread public health problem and it affects up to 1% of population of several developed countries[5]. In India, the coeliac disease was first reported in 1966 in children by Walia *et al* and in adults by Misra *et al*[6,7]. Till date, most of

the reports on CD are from northern India (Punjab, Haryana, Delhi, Rajasthan, and Uttar Pradesh)[8]. This is the first clinical profile of coeliac disease from Himachal Pradesh which is situated in the northern region of India where wheat is used as staple diet. The prevalence of coeliac disease in adults in India is not available. Prevalence of CD in children was 1/310 by Sood *et al* which is the largest field study conducted in India in school children[1]. Previously it was belief that coeliac disease is a disease of children, but now reports of coeliac disease in adults is emerging. We had 24 adults out 25 patients of coeliac disease; their mean age was 31.3 years. And one patient was 60 years old. Hankey *et al* recognised coeliac disease in adults as late as 70 years of age. In our study 68% cases were female. Coeliac disease is also common in females, but cause is not known[9]. The patients with coeliac disease will have different clinical signs and symptoms or may be asymptomatic.

We had two patients (8%) with chronic liver disease with coeliac disease, as common causes of chronic liver disease like alcohol and viral causes were ruled out; Makharia *et al* reported it in 3 (6%) out of 49 cases[8]. Two patients (8%) had isolated elevation of transaminases (SGOT/SGPT) > two times the upper limit. In the search for association of other autoimmune disorders, we had one patient with autoimmune hepatitis and one patient with hypothyroidism and one patient had type-I DM. Metabolic bone disease is also common in coeliac disease. We had one young patient with pathological fracture of femur with coeliac disease. Patients with coeliac disease can have most commonly gastrointestinal symptoms like chronic diarrhoea, bloating, anorexia, weight loss. The extra-intestinal manifestations are anaemia, osteoporosis, neuropathy, delayed puberty, infertility, growth retardation, and short stature. Anaemia is a common feature of coeliac disease, and in our study it was present in 20 (80%) cases. All patients had microcytic hypochromic anaemia caused by iron deficiency; blood loss as a cause was excluded by faecal occult blood test. In a study by Makharia *et al*, 95% of cases had anaemia at presentation[10]. Chronic diarrhoea was seen in 64% of our CD patients, whereas it was reported in 44% patients by Makharia *et al*[10], and 54.5% by Rawal *et al*[11]. Mean delay in diagnosis in our study was 4.5 yrs. and previously studies reported an average delay of 5.9 yrs[12, 13] and Agarwal *et al* reported 3.3 years in adults in a report of 31 cases[14]. In India, delay in diagnosis is due to lack of awareness among the physicians towards coeliac disease and tropical sprue. Gastrointestinal tuberculosis is considered as a major causes of chronic diarrhoea and malabsorption syndrome[8]. In histological lesions of duodenal mucosa, 8 (32%) patients were in type class IIIa, 6 (24%) had type class IIIb, and 11 (44%) of patients had type class IIIc changes. The correlation of anti-tTG level and histology was seen significant in our study. The higher the level of anti-tTG and more severe histological changes are observed in the present study. On follow-up, every patient had adherence to gluten-free diet. All became asymptomatic and mean weight gain was 7.4 kg and mean rise in haemoglobin was 3.8 gm% in every patient. Quality of life improved in every patient.

Conclusion

The coeliac disease is a major public health problem and it is widespread. Patients with coeliac disease may have typical or atypical manifestations, and sometimes are asymptomatic. A high index of suspicion is required for diagnosis. Demonstration of structural changes in mucosa of proximal small intestine in the histological study is the gold standard test. Serological study will only support the diagnosis but is not a confirmatory test. Lifelong adherence to a gluten-free diet is the only option for management.

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ORIGINAL ARTICLE

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De novo experience of a single outbreak of dengue infection at a tertiary referral centre of Uttarakhand, North India

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Abstract

***Introduction:** Emergence of dengue virus infection in the newly created state of Uttarakhand and adjoining Uttar Pradesh provided an opportunity to study the epidemic as our hospital caters to nearly 1 million population from the plains and hills. Also, with limited healthcare resources, it is necessary to identify the compelling needs in the event of resurgence and the natural course of the viral infection.*

***Method:** This is a retrospective observational study of patients hospitalised with diagnosis of dengue virus infection during the rainy season from September to November 2010 at the Himalayan Hospital, a tertiary care centre in Dehradun.*

***Results:** In the present study, 327 patients of dengue were enrolled out of which almost 90% were in the economically productive age group. Dengue fever (DF) was seen in 271 (82.8%) and dengue haemorrhagic fever (DHF) was seen in 56 (17.1%). Of the 178 (54.4%) and 149 (45.5%) patients with primary and secondary dengue infection, 12 (6.5%) and 44 (29.9%) developed DHF respectively. Bleeding was observed in less than a fifth (18.9%) patients; however, platelet concentrates were transfused in nearly four times this number. Platelet recovery and hospitalisation was significantly prolonged in those with DHF as compared to DF ($p<0.05$). Widespread liver involvement (94.0%), macrocytosis (32.1%), hyponatraemia (19.5%) and acute renal insufficiency (14.3%) were the unusual observations.*

***Conclusion:** Low incidence of bleeding, unusual bleeding manifestations, widespread fear, indiscriminate platelet transfusion, and uncommon complications bereft of mortality were the major highlights. Pooling of data of adult dengue patients from different regions will help in the understanding and development of evidence based guidelines for management. Our data aims at contributing towards this goal.*

***Key words:** Dengue fever, dengue haemorrhagic fever, thrombocytopenia, primary dengue infection, secondary dengue infection.*

Introduction

Dengue fever (DF), and especially the more severe manifestation, dengue haemorrhagic fever (DHF) ranks high in public health significance among the new and newly emerging infectious diseases. It is considered to be the most important arthropod-borne viral disease[1]. Globally, more than 2.5 billion people are at risk, with nearly half-a-million hospitalisations and 5% deaths due to dengue viral infections each year. The major brunt (90%) of this illness is borne by children (< 15 years)[2]. Cases of DHF, mainly responsible for mortality, are increasing and outbreaks are becoming a regular feature in the South-East Asia region[3].

The relationship of India with dengue has been long and intense. The first epidemic of clinically dengue-like illness was recorded in the south Indian city of Madras (now known as Chennai) in 1780. The dengue virus was isolated for the first time almost simultaneously in Japan and Calcutta in 1943-1944. The first virus-proven epidemic of dengue fever occurred along the east coast of India in 1963-1964; later it spread to the whole of the country. In 1996, North India witnessed the first epidemic of the severe form of the illness, the dengue haemorrhagic fever/dengue shock syndrome (DSS). In recent decades, the geographical distribution of the virus and the mosquito vector has expanded, the epidemic activity increased, and DHF has emerged in new geographical regions[4]; the reasons of which are complex and not fully understood. Presumably, demographic, social, and public health infrastructure changes in the past decades have contributed greatly to this phenomenon[5]. Demographic factors like uncontrolled population growth, unplanned urbanisation resulting in substandard housing and poor solid waste disposal and need for water storage aided vector proliferation and hence increased exposure. Enhanced awareness and availability of laboratory facilities have made the recognition and differentiation of the infections easy.

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Dengue infection occurs in three forms – DF, DHF, and DSS. According to the WHO case definition, DF is defined as an acute febrile illness with two or more manifestations among headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, leucopenia, supportive serology, occurrence at the same location and time of other confirmed cases[6]. DHF is defined as a 2 to 7 day acute febrile illness with bleeding, thrombocytopenia and evidence of plasma leakage. When all features of DHF are present along with evidence of circulatory failure, the patient is categorised as DSS[7].

Here, we share our experience at a tertiary referral centre during an epidemic of dengue virus infection affecting the population of the newly formed state of north India and its adjoining areas. We have also tried to highlight the demographic factors that plagued this outbreak.

Methodology

All adult (>18 years) consecutive out- and in-patients at the Himalayan Hospital, Dehradun, diagnosed with dengue virus infection, presenting between July and November 2010, either from primary referral facilities or in our hospital were enrolled for the study. Demographic, clinical, haematological, and biochemical laboratory data was recorded in a pre-designed format. Serology for dengue antibody was done in all cases using SD Bioline Dengue Duo (Dengue NS1 Ag; IgM/IgG test). This test has 84% sensitivity, 98% specificity, 99% positive and 68% negative predictive value. Patients with IgG positive were labelled as having secondary dengue infection. Those with thrombocytopenia diagnosed in the past or with a concomitant cause contributing to thrombocytopenia, viz., malaria, septicaemia, chemotherapy, etc., were excluded. Cases were classified as DF, DHF, or DSS as per WHO case definition[6,7]. Other investigations were carried out as and when indicated. Platelet recovery was considered if two consecutive counts from samples drawn 24 hours apart showed an increasing trend, or the platelet count increased beyond 50,000/cu mm when less at presentation. The data was computer-processed using IBM-SPSS software (version 19).

Results

Of the 342 patients with dengue virus infection, presenting to Himalayan Hospital during the above-mentioned period, 15 were excluded due to concomitant malarial infection and the remaining 327 were studied. Of these, 302 (92.3%) belonged to the plains and 25 (7.6%) came from the hilly regions of Uttarakhand. Almost 90% of those affected were in the economically productive age-group and males constituted nearly three-fourth (n = 244; 74.6%) of the study population.

Although sporadic cases were diagnosed regularly from July 2010, the epidemic started in the month of September and ended in November with maximum incidence in October (64.8%). Isolated positivity of NS1 was encountered in 58.4% (n = 191), of NS1 and IgM in 44.6% (n = 146) and of IgM and IgG in 45.5% (n = 149) cases. Of all serologically proven cases of dengue, 149 (45.5%) were having secondary dengue infection and 178 (54.4%) had primary dengue infection. DF was diagnosed in 271 (82.8%), while 56 (17.1%) cases had DHF. Of the 149 patients with secondary dengue infection 105 (70.4%) developed DF and 44 (29.5%) developed DHF. Of the 178 patients with primary dengue infection, 166 (93.2%) developed DF and 11 (6.1%) developed DHF (OR 6.16; 95% CI 3.77-10.06; $p < 0.001$). Table I shows clinical and laboratory findings of patients with dengue fever (DF) and dengue haemorrhagic fever (DHF).

A history of fever was obtained in all; however 217 (66.3%) had fever at presentation. The remaining (n = 110; 33.6%) had a history of fever for 5 to 6 days prior to hospitalisation and consulted us either for thrombocytopenia (n = 51), and/or abdominal pain, vomiting, and myalgia (n = 58). Duration of fever at presentation varied from 1 day to 1 month. Fever of short duration (< 10 days) was reported by 320 patients; 7 had prolonged fever of whom 4 were afebrile at presentation (platelet count < 20,000/cumm: n = 1; 20-50,000/cumm: n = 3). The remaining patients who were febrile had less marked thrombocytopenia (platelet count > 50,000/cumm). However, none of these patients had any bleeding manifestation.

Table II shows the platelet counts in relation to bleeding manifestations. One of the remarkable observations in our study was that almost three-quarter of all the patients received platelet concentrates while bleeding was observed in 62 (18.9%) patients. Melaena was the commonest form (n = 32; 51.6%) of manifest bleeding followed by gum bleed (n = 10; 16.1%), epistaxis (n = 9; 14.5%) and haematemesis (n = 5; 8.0%). Bleeding per vaginum was encountered in 9 out of the 83 (10.8%) women in our study cohort; none was menstruating at the time of infection. Other less common forms of bleeding are shown in Figure 1.

Overall, the platelet recovery time was 2.6 ± 1.8 days (range 1 - 7). Platelet recovery and hospitalisation was significantly prolonged in DHF as compared to DF (3.3 ± 1.5 vs. 2.1±1.2; p = 0.003 and 5.1 ± 1.3 vs. 4.1 ± 1.5 days; p = 0.001). Duration of hospitalisation was prolonged in patients suffering from DHF as compared to those with DF because it took more time for their platelets to recover as well as for subsidence of the symptoms like

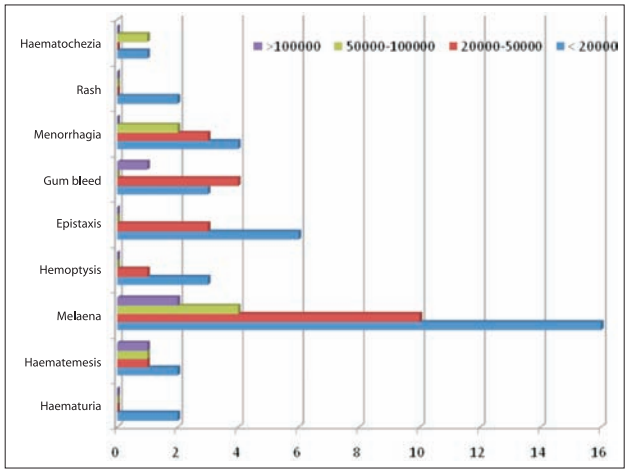

Fig. 1: *Bleeding manifestations in patients with thrombocytopenia.*

myalgia, abdominal pain, and vomiting. Also, a slight, albeit statistically insignificant, prolongation of platelet recovery time and duration of hospitalisation in patients suffering from chronic diseases like DM, COAD, and elderly patients was observed. No difference was seen in terms of disease course/outcome in the form of preventing bleeding or decreasing the duration of hospital stay if patients received the so called *prophylactic platelet transfusion*.

One important observation emanating from our study was the difference in patients from hilly regions and plains. Those from hilly areas presented late (n = 25) when the number of patients with dengue was decreasing from plains, i.e., the latter half of November. Most (n = 22) of them were afebrile, and thrombocytopenia was not marked. Abdominal pain and myalgia were the presenting features in two-third; half of them had secondary dengue infection.

Other organs involved in serologically positive cases of dengue were the liver (n = 310; 94.8 %) and kidneys (n = 47; 14.3%); ARDS (n = 4; 1.2%), and myocarditis (n = 1; 0.3%) were other unusual presentations. Macrocytosis was observed in the peripheral smears of 105 (32.1%) patients while hyponatraemia was documented in 64 (19.5%) patients. There was no mortality in our study group.

Discussion

The incidence of dengue has increased 30-fold in 50 years (1960-2010) and is deemed only second in importance to malaria[8]. This increase is believed to be due to a combination of disproportionate population growth, unplanned urbanisation, increased international travel, and global warming[9]. In the present study, male to female ratio was 3:1 in contrast to the earlier observation[9] but is

Table I: Clinical and laboratory findings in patients with dengue fever (DF) and dengue haemorrhagic fever (DHF).

Parameters	DF (n = 271)	DHF (n = 56)	p value	Chi-Sq value	Likelihood ratio	95% CI	Odds ratio
Clinical features							
Fever	199 (73.4%)	18 (32.1%)	< 0.001	68.005	64.28	0.12-0.28	0.178
Headache	74 (27.3%)	16 (28.5%)	0.785	0.074	0.074	0.68-1.67	1.065
Arthralgia	33 (12.1%)	9 (16.0%)	0.288	1.130	1.076	0.77-2.39	1.358
Myalgia	122 (45.0%)	27 (48.2%)	0.256	1.289	1.286	0.84-1.9	1.266
Bleeding	38 (14.0%)	24 (42.8%)	< 0.001	50.277	42.83	2.94-7.18	4.599
Retro-orbital pain	21 (7.7%)	8 (14.2%)	0.012	6.242	5.493	1.16-3.9	2.130
Diarrhoea	28 (10.3%)	16 (28.5%)	< 0.001	28.899	24.278	2.22-5.93	3.625
Constipation	23 (8.4%)	16 (28.5%)	< 0.001	31.923	26.244	2.42-6.72	4.031
Nausea	65 (23.9%)	20 (35.7%)	0.006	7.658	7.243	1.19-2.82	1.830
Vomiting	99 (36.5%)	25 (44.6%)	0.208	1.583	1.563	0.86-1.97	1.303
Abdominal pain	86 (31.7%)	22 (39.2%)	0.132	2.272	2.224	0.91-2.10	1.380
Vertigo	23 (8.4%)	6 (10.7%)	0.263	1.254	1.175	0.75-2.79	1.450
Sinusitis	25 (9.2%)	6 (10.7%)	0.892	0.018	0.018	0.53-2.08	1.049
Itching	90 (33.2%)	18 (32.1%)	0.998	0.00	0.00	0.65-1.54	1
Rash	64 (23.6%)	14 (25.0%)	0.608	0.264	0.260	0.71-1.80	1.130
Haematological parameters							
PCV > 45	41 (15.1%)	16 (28.5%)	0.001	0.001	10.848	1.42-3.65	2.277
WBC < 4,000	114 (42.0%)	19 (33.9%)	0.103	0.103	2.707	0.46-1.07	0.702
PLT < 100,000	244 (90.0%)	56 (100%)	< 0.001	< 0.001	21.268	-	-

Table II: Thrombocytopenia, bleeding, and transfusion in dengue infection.

Platelet count (per cumm)	No. of patients	Bleeding		Received platelet transfusion
		Present	Absent	
< 20,000	109	30 (27.5%)	79 (72.5%)	87 (79.8%)
20,000 - ≤ 50,000	120	24 (20%)	96 (80%)	84 (7%)
50,000 - ≤ 100,000	70	5 (7.1%)	65 (92.9%)	65 (92.9%)
> 100,000	27	3 (11.1%)	24 (88.8%)	1 (3.7%)
Total	327	62(18.9%)	265 (81%)	237 (72.4%)

in concordance with a study from Delhi[10]. Dengue can be life-threatening in people with chronic diseases such as diabetes and asthma[9]. In our study, even though there was no death due to dengue in those with underlying chronic disease, platelet recovery time and duration of hospitalisation was prolonged indicating increased morbidity.

A high incidence of bleeding is reported in literature[11,12]; however, in the present study, bleeding manifestations were not a prominent feature despite almost universal thrombocytopenia (91.7%). This finding is in accordance with the findings of Sumarmo[13]. Almost three-quarter platelet transfusions were apparently unnecessary (n = 175). A few of these transfusions (n = 56; 31.9%) were pre-hospitalisation transfusions prior to referral leading to platelet recovery at hospitalisation. Others may have presented late in the natural course of the illness; however, the rampant fear of thrombocytopenia among the patients as well as in the medical fraternity was a remarkable feature of this epidemic. In our study, melaena was the major bleeding manifestation in contrast to other studies. The high incidence of gastrointestinal bleed in our region may be attributed to the high prevalence of acid-peptic disease in this region. Primary dengue infection was observed in 54.4% patients in our cohort, still significant

Table III: Clinical and laboratory features in studies of hospitalised patients with dengue infection.

Study Country	Wichmann[11] Thailand	Malavige[12] Sri Lanka	Pervin[19] Bangladesh	Seet[20] Singapore	Gonzalez[21] Cuba	Kularatne[22] Sri Lanka	Lai[23] Taiwan	Harris[24] Nicaragua	Ours India
Number studied	347	108	97	34	76	183	13	614	327
DF/DHF (%)	37/63	31/69	79/18	97/3	0/100	NS	54/46	44/56	82.8/17.1
Primary dengue infections (%)	20	34.3	47	97	NS	23	NS	27	54.4
Secondary dengue infections (%)	80	65.7	53	3	NS	77	NS	73	45.5
Clinical features									
Myalgia (%)	8	76	85	NS	76	74	77	64	45.5
Arthralgia (%)	8	57	68	NS	74	NS	61	62	12.8
Flushed appearance (%)	NS	42	NS	53	NS	62	NS	NS	NS
Vomiting (%)	59	64	36	38	59	NS	15	50	37.9
Diarrhoea (%)	NS	29	NS	41	29	NS	15	16	13.4
Abdominal pain (%)	NS	17	6	21	49	NS	54	46	33.0
Enlarged liver (%)	40	45	13	0	1.8	NS	21	4	45
Splenomegaly (%)	NS	0.02	NS	NS	13	NS	NS	NS	5
Bleeding manifestations (%)	36	42	16	27	100	15	46	37	18.9
Pleural effusions/ascites (%)	NS	11	5	NS	20	3	38	NS	17.1
Shock (%)	12	14	1	0	24	0.005	15	10	0
Haematological features									
Thrombocytopenia (%)	NS	79	23	85	100	90	85	NS	91.7
Raised haematocrit (%)	NS	22	17	1	93	91	39	NS	17.4
WBC < 4×10^9/l (%)	NS	31	NS	82	71	NS	61	NS	40.6
Received IV fluids (%)	NS	74	NS	NS	NS	NS	NS	NS	100
Given platelet concentrates (%)	NS	12	NS	NS	NS	NS	NS	NS	72.4
Given FFP (%)	NS	5.5	NS	NS	NS	NS	NS	NS	2.2
Mortality rate (%)	0.5	3.7	NS	0	2.6	0.02	0	0.001	0

NS = Not stated; FFP = Fresh frozen plasma; DF = Dengue fever; DHF = Dengue haemorrhagic fever.

severe complications were not evident. This may represent the development of immunity in adult population and also infection by a non-virulent strain of dengue virus. Table III illustrates the presentation of dengue from different countries across the world.

The late presentation of the patients hailing from hilly areas may be attributed to the movement of population from plains to their home towns in hills (carrying with themselves the subclinical form of infection contracted in the plains) for celebrating the festival of Diwali, which coincided with the outbreak of dengue. Atypical forms of dengue infection may present with hepatic and renal dysfunction. Although liver is not the target organ of dengue virus, several pathological findings including fatty change, centrilobular necrosis, and monocyte infiltration in the portal tract, have been reported[14]. Renal injury comprising azotaemia, proteinuria, glomerulonephritis, acute kidney injury (AKI) and haemolytic uraemic syndrome have been reported in dengue patients[15]. In the present study, 47 (14.3%) patients had mild-to-moderate renal injury without shock. Hyponatraemia and macrocytosis observed in 19.5% and 32.1% cases respectively in our study, is presumably the first emphatic report in the literature. Macrocytosis can be attributed to the widespread liver damage seen in our study. Hyponatraemia was seen presumably due to vomiting and diarrhoea and haemoconcentration due to intra- and extra-vascular hypovolaemia.

Conclusion

De novo occurrence of an epidemic of an infectious disease in this geographical region is in concordance with the observations made by the co-authors in their earlier studies[16,17]. Also, variable presenting features are in accordance with our earlier study with regard to vivax malaria[18]. During this time period, the entire north India was dealing with a similar epidemic and the data published elsewhere is in concordance with our study. Migration of labourers, construction of the Tehri dam in the Garhwal region, improvement in the road links, and increase in th number of pilgrims to this hilly region with the consequent problems such as water logging, and lack of proper sanitation may have caused an ecological shift in vector proliferation leading to an emergence of this disease in this region. Also, possible genotypic abnormalities that the virus or its carrier may have acquired over decades of aggression of insecticides, injudicious usage of antibiotics, and possible co-infection with other viruses could be responsible for the atypical presentations. Another possibility is the co-infection with newer plasmodial species in particular, something that may have occurred and gone unrecognised by conventional testing techniques.

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ORIGINAL ARTICLE

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Highly sensitive C-reactive protein in metabolic syndrome

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Abstract

Background: Metabolic syndrome is known to predispose to atherosclerosis. C-reactive protein, a marker of systemic inflammation is significantly associated with the atherosclerotic process.

Methods: We prospectively studied the relationship between high-sensitivity C-reactive protein (hs-CRP) with various components of metabolic syndrome in 91 patients with metabolic syndrome at our tertiary care centre in South India.

Results: The mean age of patients was 57.5 ± 9.8 years; there were 67 (73.6%) males. On univariate analysis, hs-CRP was found to be significantly increased in patients with diabetes mellitus (p < 0.021) and those with abnormal waist circumference (p<0.003). There was no significant association between hs-CRP and high triglycerides, hypertension, and reduced high density lipoprotein cholesterol. Further, hs-CRP increased significantly with increasing number of components of metabolic syndrome (p< 0.008).

Conclusions: Measurement of hs-CRP can be used as a surrogate marker of chronic inflammation in patients with metabolic syndrome

Key words: Metabolic syndrome, hs-CRP, India.

Introduction

The metabolic syndrome[1] is the concurrence of hyperglycaemia, mild dyslipidaemia, hypertension, and visceral obesity that substantially increases the risk of developing cardiovascular diseases and type 2 diabetes mellitus[2]. Recent studies have shown that in both developed and developing countries there is a continuing epidemic of diabetes mellitus and obesity, and hence the occurrence of metabolic syndrome[3]. Because of the increased risks for morbidity and mortality associated with this syndrome, the knowledge of its dimension is critical for planning prevention, and health care interventions.

C-reactive protein (CRP) is a marker of low grade chronic systemic inflammation. Normal high-sensitivity CRP (hs-CRP) varies from 0 - 5 mg/L in healthy young adults[4] and is significantly associated with the metabolic syndrome and its components. It is highly predictive of subsequent risk of cardiovascular events and diabetes mellitus in apparently healthy men and women. Indeed, higher CRP levels provide additional prognostic information on cardiovascular risk in patients with metabolic syndrome[5]. Very little has been documented on this topic from India. The present study was designed to study the relationship of hs-CRP with the components of metabolic syndrome.

Material and methods

Patients aged above 20 years presenting to the Medicine out-patient service and those admitted to the medical wards at our tertiary care centre in South India were included in the present study. The data were recorded from each subject with an in-person interview by administering a specific questionnaire. The components of metabolic syndrome were defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria considering abdominal obesity as per World Health Organization (WHO) guidelines for South Asians[6,7]. Height and weight were measured. Waist circumference was measured using a non-elastic measuring tape at the highest level of iliac crest with the patient standing with feet 1 foot apart[8]. Systolic and diastolic blood pressure was measured by sphygmomanometer. Individuals reporting a history of hypertension and current antihypertensive medication use were defined as having hypertension regardless of the blood pressure values measured at the time of evaluation. Diabetes mellitus was diagnosed as per the American Diabetic Association (ADA) diagnostic criteria[9] and/or concomitant anti-diabetic treatment, regardless of the measured glucose values.

The study protocol was approved by the institutional ethics committee before initiation of the study. Informed consent was obtained from each patient before enrolling.

In all the patients, a peripheral venous blood sample was drawn in the morning after 8 - 10 hours of fasting, to measure venous plasma glucose, serum total cholesterol, serum high density lipoprotein (HDL) cholesterol, and serum triglyceride levels. Serum glucose was measured by the glucose oxidase method; plasma triglycerides, total

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cholesterol and HDL-cholesterol were measured by enzymatic colorimetric assay using Cobas 6000 autoanalyser (Roche, Germany). Serum hs-CRP levels were determined by particle enhanced immune-turbidometric assay using Cobas 6000 Autoanalyser with dedicated reagents (Roche, Germany)[10].

The data were analysed using SPSS version 15 (SPSS Inc.). The median hs-CRP levels were compared in patients with or without various components of metabolic syndrome using Mann-Whitney U test.

Results

Ninety-one patients satisfying the criteria for metabolic syndrome were studied. Their mean age was 57.5 ± 9.8 years; there were 67 (73.6%) males. The patients were divided into three different age groups: less than 40 years (n = 3, 2 males); 40 - 60 years (n = 55, 43 males); and older than 60 years (n = 33, 22 males). Out of 91 patients studied, 78 (86%) had raised fasting glucose, 77 (85%) had hypertension, 82 (90%) had central obesity, 75 (82%) had raised serum triglycerides, and 48 (53%) had low serum HDL levels. The distribution of components of metabolic syndrome in different genders is given in the Table I.

Table I: Components of metabolic syndrome in different genders.

Variable	Elevated fasting glucose (%)	Hypertension (%)	Obesity (%)	High serum triglycerides (%)	Low serum high density lipoprotein cholesterol (%)
Males (n = 67)	60 (89.5)	46 (68.6)	58 (86.5)	56 (83.5)	28 (41.7)
Females (n = 24)	20 (83.3)	17 (70.8)	21 (87.5)	18 (75)	17 (70.8)
Overall	80 (87.9)	63 (69.2)	79 (86.8)	74 (81.3)	45 (50.3)

Correlation of components of metabolic syndrome with hs-CRP

In 78 diabetic patients (53 of them were known diabetic patients) included, the median hs-CRP was 1.3 mg/L as compared to 13 non-diabetic patients which was significant ($p < 0.027$). In 77 hypertensive patients the median hs-CRP was 1.2 compared to non-hypertensive group where the median hs-CRP was 1.8 mg/L. The difference was not significant. In 82 patients having abnormal waist circumference criteria, the median hs-CRP was 1.4 mg/L compared with patients having normal waist circumference which was also highly significant ($p < 0.013$). In 75 patients with high triglyceride and 16 patients without these criteria, the median hs-CRP values were almost similar without much significant difference. In 48 patients with low HDL and 43 patients with normal HDL, the median hs-CRP values were almost equal with no significant relation with this group. The results of univariate analysis are shown in Table II.

Table II: Univariate analysis: Comparison of hs-CRP levels between patients with and without various components of metabolic syndrome.

Metabolic syndrome component	hs-CRP level (mg/L) [Median (IQR)]	p-value
Obesity		
Yes (n = 82)	1.4 (0.7-2.7)	
No (n = 9)	0.8 (0.6-0.8)	0.013
Diabetes mellitus		
Yes (n = 78)	1.3 (0.7-2.7)	
No (n = 13)	0.7 (0.6-1.2)	0.027
Low HDL		
Yes (n = 48)	1.2 (0.7-2.6))	
No (n = 43)	1.1 (0.7-2.0)	0.820
High TG		
Yes (n = 75)	1.2 (0.7-2.4)	
No (n = 16)	1.1 (0.7-1.8)	0.834
High systolic BP		
Yes (n = 76)	1.2 (0.7-2.6)	
No (n = 15)	1.4 (0.7-2.4)	0.520
Hypertension		
Yes (n = 77)	1.2 (0.7-2.4)	
No (n = 14)	1.1 (0.7-1.8)	0.501
High diastolic BP		
Yes (n = 46)	1.1 (0.7-2.7)	
No (n = 45)	1.4 (0.7-2.4)	0.653

hs-CRP = C-reactive protein; IQR = interquartile range; HDL = high density lipoprotein cholesterol; TG = serum triglycerides; BP = blood pressure.

The metabolic syndrome patients were further grouped in terms of number of criteria satisfied. Out of 91 patients, 44 (48%) were satisfying 3 criteria, 27 (30%) 4 criteria and 20 (22%) five criteria. In the minimal 3 criteria group (which is required for the metabolic syndrome) majority (15%) of the patients were in the diabetes, hypertension, and abdominal obesity group ($p < 0.01$) making this the most common combination for metabolic syndrome.

We measured the hs-CRP levels with increasing components of metabolic syndrome. With minimum three components of metabolic syndrome, the median value was 1.2 mg/L; with 4 components, the median value was 1.8 mg/L; and with all the five components, the median value was 2.2 mg/L ($p < 0.008$) (Figure 1).

The distribution of each component of the metabolic syndrome according to the modified NCEP-ATPIII criteria for metabolic syndrome in other published studies and our study is depicted in Table III[11-13].

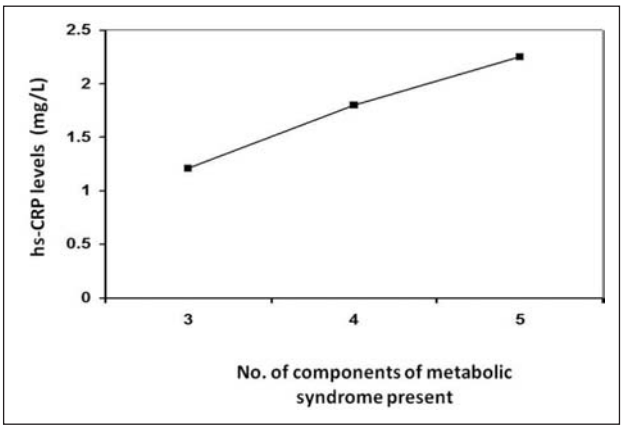

Fig. 1: *Relationship of highly sensitive c-reactive protein levels with presence of increasing number of components of metabolic syndrome.*

Table III: Distribution of each component of the metabolic syndrome in various published studies.

Study (reference)	Elevated fasting glucose (%)	Hypertension (%)	Obesity (%)	High TG (%)	Low HDL (%)
Bo *et al*[11] n = 1877	18	66	36	30	8
Florez *et al*[12] n = 190	31	70	80	32	46
Ramachandran *et al*[13] n = 475	26	55	31	45	65
Present study n = 91	88	69	86	81	49

n = No. of subjects studied; TG = serum triglycerides; HDL = high density lipoprotein cholesterol.

Discussion

Traditional cardiovascular risk factors such as central obesity, high blood pressure, and diabetes – all components of metabolic syndrome – have been associated with increased levels of CRP. Therefore, this marker of low grade inflammation may play a role in the pathogenesis of cardiovascular diseases (CVD)[4].

A number of studies show that both metabolic syndrome and elevated CRP are associated with increased incidence of cardiovascular events. In the epidemiological studies like West of Scotland Coronary Prevention Study, an 18-year follow up of 14,719 initially healthy American women, and in the Framingham Offspring Study it was shown that metabolic syndrome and CRP are associated with increased cardiovascular morbidity and mortality[14-16].

CRP is released by the liver following stimulation by interleukin-6, and is also locally produced in atheromatous lesions. Although most studies relied on a single measurement of CRP, this is not expected to affect the results, as CRP levels have been shown to be stable with little or no diurnal variation, making CRP the most commonly used and best standardised inflammatory marker of cardiovascular and metabolic disorders[17].

In the current study, we evaluated the relationship of CRP with the components of metabolic syndrome in in-patients and out-patients of our hospital. Metabolic syndrome was diagnosed in them using modified NCEP-ATP III criteria[6]. The San Antonio Heart Study suggested that although both definitions (WHO and NCEP-ATPIII) were predictive in the general population, the simple NCEP-ATP III definition tended to be more predictive in lower-risk subjects[18]. Hence we used the modified NCEP-ATP III criteria for our study.

The prevalence of metabolic syndrome in men and women has been varyingly addressed. In other published studies the prevalence of metabolic syndrome was more common in females than males[13]. In our study with 91 patients, metabolic syndrome was found to be more common in males (74%) than in females (26%). Ours was a hospital based study and hence the number of males is likely to be high reflecting a social bias.

Majority of the patients with metabolic syndrome (60.4%) were in the age group of 40 - 60 years, the next major group was patients of > 60 years (36.3%). Only 3 patients (1.09%) were in the age group of < 40 years. In adults in the United States participating in the third National Health and Nutrition Examination Survey (NHANES III) prevalence of metabolic syndrome was 22 per cent, with an age-dependent increase (6.7%, 43.5%, and 42% for ages 20 to 29, 60 to 69, and > 70 years, respectively)[19]. Similar observations were reported by Gupta *et al* in their population based study[20]. This is due to the increasing prevalence of diabetes, hypertension, and dyslipidaemia in the ageing population.

When we compared the mean hs-CRP levels of each of the age groups, (< 40, 40 - 60, and > 60 years) it was found to be 0.7, 1.4, and 2 mg/L showing a definite increase with age. In Korean population, it was observed that in participants aged 40 - 69 years, the mean hs-CRP level increased according to age and was observed to be 1.2, 1.5 and 1.6 mg/L for the age groups 40-49, 50-59, and 60-69 years, respectively[21]. The hs-CRP value increases with age, presumably reflecting the increasing incidence of sub-clinical inflammation as the age advances. It is shown that hs-CRP is involved in the pathogenesis of atherosclerosis and atherothrombosis. As the age progresses, there is increased atherosclerosis and hence hs-CRP levels also will be moderately elevated.

Our study group had more number of patients with diabetes mellitus when compared with other studies. This was because ours was a hospital-based study while all

others were population-based studies. In our study group we had central obesity being more prevalent reflecting the increased prevalence of this abnormality in Indian as well as South-Asian population.

Association of highly sensitive C-reactive protein with components of metabolic syndrome

Our analysis revelaed that there was a significant association between hs-CRP and the components of the metabolic syndrome. This was more so with central obesity (1.4 vs 0.8 mg/L, p = 0.013), and with diabetes mellitus (1.3 vs 0.7 mg/L, p = 0.027). Several studies have showed that central obesity is associated with high hs-CRP levels[22,23]. In some other studies, it was observed that diabetes mellitus was associated with elevated hs-CRP levels[24,25]. A positive association between high blood pressure and elevated hs-CRP was noted in some studies[26,27], but our study did not show any association between hypertension and elevated hs-CRP level.

In our study, central obesity is shown to have the highest association with high hs-CRP levels (p = 013). Florez *et al*[12] also found that abdominal obesity was the single most important component associated with increased hs-CRP levels in 190 subjects with metabolic syndrome (p = 0.001)[12]. In the Insulin Resistance Atherosclerotic Study (IRAS)[28], a strong association was found between hs-CRP and measures of body fat (p = 0.0001). It is well documented that the synthesis of CRP in the liver is under the control of interleukin-6 and tumour necrosis factor-alpha (TNF-α), cytokines that are released or induced by adipose tissue, which could be the link between obesity and the elevation of CRP levels[5]. Hence, the most important determinant of the systemic chronic low grade inflammation is probably central obesity.

In our study, we also found that there was higher median concentration of hs-CRP with increasing number of components of the metabolic syndrome. Patients satisfying 3, 4, and 5 criteria had a median hs-CRP of 1.21, 1.80, and 2.29 mg/L respectively. As expected there was significant positive linear association with number of abnormal features of the syndrome (p = 0.008). Bo *et al*[11] also found similar findings, the mean hs-CRP for those with 0, 1, 2, 3, 4, 5 components of the metabolic syndrome were 1.9, 1.8, 2.9, 4.1, 4.1, and 5.3 mg/L (p = 0.001). This suggests the fact that higher the number of components of metabolic syndrome in a patient, higher the risk of cardiovascular events.

More recently it was considered that measurement of CRP should be added in the metabolic syndrome components as it was closely related with other components of the syndrome[29]. The treatment of several components of metabolic syndrome may have beneficial effects in preventing cardiovascular disease. Therefore, if subclinical inflammation is indeed another aspect of metabolic syndrome, anti-atherogenic treatment in the form of anti-platelets and statins could be sought due to their pleotrophic effects. Additionally, the advantage of non-pharmacological interventions, such as weight reduction or regular practice of exercise, may be translated into lower CRP levels due to reduced inflammation, thus providing benefits that go beyond solely decreasing glucose levels or obesity prevalence[8].

In conclusion, a positive correlation was found between hs-CRP and the components of metabolic syndrome like central obesity and diabetes mellitus. Highly significant correlation was present between central obesity and CRP. There was a linear increase in hs-CRP with increasing number of metabolic syndrome components. Hence hs-CRP can probably be used as a surrogate marker of chronic inflammation in patients with metabolic syndrome.

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"Mind means the turmoil, the illness, the disease;
mind means the tense, the anguished state.
When silence comes, mind disappears;
when mind is there, silence is no more.
So there cannot be any silent mind, just as there cannot be any healthy disease.
Is it possible to have a healthy disease?
When health is there, disease disappears.
Silence is the inner health;
mind is the inner disease, inner disturbance."

– Osho, the Zen master.

REVIEW ARTICLE

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Cushing's syndrome – An update in diagnosis and management

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Abstract

Cushing's syndrome results from chronic exposure to excess glucocorticoids and if remains undiagnosed/untreated is associated with increased morbidity and mortality. The classical clinical features of Cushing's syndrome are not always present and a high index of suspicion is required in many cases. Furthermore Cushing's syndrome should be differentiated from pseudo-Cushing's syndrome seen in association with obesity, chronic alcoholism, depression and acute illness of any type. This review will highlight the clinical features, diagnostic approach, and current treatment strategies for timely diagnosis and treatment of Cushing's syndrome.

Introduction

Cushing's syndrome results from chronic exposure to excess glucocorticoids and if remains undiagnosed/untreated is associated with increased morbidity and mortality[1,2]. It was first described by Harvey W Cushing in 1932. Iatrogenic Cushing's syndrome resulting from long-term use of exogenous glucocorticoids is the most common cause of Cushing's syndrome. Endogenous Cushing's syndrome is broadly classified into ACTH-dependent and ACTH-independent, and is more common in women than in men[3] (Table I). The term Cushing's disease is reserved for pituitary dependent Cushing's syndrome. ACTH-dependent Cushing's syndrome includes Cushing's disease, ectopic ACTH syndrome, and ectopic CRH syndrome. While ACTH-independent Cushing's syndrome includes adrenal adenoma, adrenal carcinoma, primary pigmented nodular adrenal hyperplasia (Carney's syndrome), macronodular adrenal hyperplasia, Mc-cune-Albright syndrome and aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1B, leutenising hormone)[4-7]. The incidence of pituitary-dependent Cushing's syndrome is 5 to 10 cases per million population per year while that of ectopic ACTH syndrome parallels that of bronchogenic carcinoma. The common causes of ectopic ACTH syndrome include small cell lung carcinoma, carcinoids (pancreatic, bronchial, thymic), medullary carcinoma of thyroid, pheochromocytoma, and rarely carcinoma of the prostate, breast, ovary, gall bladder, and colon[5]. Overall, ACTH-dependent causes account for 80 - 85% of cases and of these 80% are due to Cushing's disease, and 20% are due to ectopic ACTH secretion and the rest are ACTH independent[1].

Table I: Cushing's syndrome – aetiology.

ACTH-dependent Cushing's syndrome (80%)
1. Pituitary dependent Cushing's syndrome: 68%
2. Ectopic ACTH syndrome: 12%
3. Ectopic CRH syndrome: rare (<1%)
ACTH-independent Cushing's syndrome (20%)
1. Adrenal adenoma: 10%
2. Adrenal carcinoma: 8%
3. Macronodular adrenal hyperplasia: rare (1%)
4. Micronodular adrenal hyperplasia: rare (<1%)
5. Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1B, leutenising hormone): rare (<1%)

Clinical features

The classical clinical features of Cushing's syndrome include centripetal obesity, moon facies, hirsutism, plethora, red-purple striae, bruising, proximal muscle weakness, psychiatric disturbances, osteoporosis, and menstrual irregularity[3]. Glucocorticoid excess causes obesity by stimulating adipogenesis through transcriptional activation of adipocyte differentiation gene including lipoprotein lipase, glucorol-3-phosphate dehydrogenase and leptin. Furthermore, excess glucocorticoid by reducing CRH (which normally has anorexic effect) causes increase in appetite and weight gain. The most discriminatory features that help in distinguishing Cushing's syndrome from simple obesity include signs and symptoms of protein catabolism, i.e., proximal muscle weakness, red-purple striae, bruising, cuticular/pulp atrophy and osteoporosis. However, these gross clinical symptoms and signs are not always present and a high index of suspicion is required in many cases. Glucose intolerance and overt diabetes mellitus is seen in up to one-third of cases. Glucocorticoid increases hepatic glucose output by activation of key gluconeogenesis enzyme

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phosphoenolpyruvate carboxykinase. Hypertension is seen in up to 75% of cases by increasing cardiac output, activation of rennin-angiotensin system by increasing hepatic production of angiotensinogen, decreasing synthesis of vasodilatory nitric oxide, enhancing the pressor sensitivity to endogenous catecholamines and by specificity spillover with activity on mineralocorticoid receptors. There is 2 - 5% prevalence of unsuspected Cushing syndrome in patients with poorly controlled diabetes mellitus[8-10], 3% in patients with osteoporosis[11], and 9% among patients with incidental adrenal mass of more than 2 cm[12]. Since clinical features of polycystic ovary syndrome overlap with those of Cushing's syndrome, it should be ruled out in such patients[13]. Less common and unappreciated clinical features of Cushing's syndrome includes exophthalmos, chemosis, lisch nodule and central serous chorioretinopathy[14-16]. Clinical features like cataract, increased intraocular pressure, benign intracranial hypertension, aseptic necrosis of femoral head, osteoporosis, and pancreatitis are more common in iatrogenic Cushing's syndrome; whereas hypertension, hirsutism, and oligomenorrhoea are rare.

In children, adrenal causes account for 65% of all cases with Cushing's syndrome[17]. The growth retardation, obesity and delayed puberty is the most common presenting feature[18]. However, adrenal androgen excess usually seen in patients with adrenocortical carcinoma may result in precocious pseudopuberty. Muscle weakness is less common reflecting the effect of growing age. Depression is less common than adults and these children may show compulsive diligence – and actually do quite well academically.

Thus, it requires a high index of clinical suspicion for making an early diagnosis of Cushing's syndrome and it should be ruled out in patients with symptoms/signs/clinical diagnosis as summarised in Table II.

Table II: Screening of Cushing's syndrome.

1. Central obesity with features of protein catabolism
   - Facial plethora
   - Cuticular atrophy
   - Cutaneous wasting with bruise and ecchymosis
   - Wide violaceous striae (>1cm)
   - Proximal myopathy
2. Short stature with obesity and delayed bone age
3. Metabolic syndrome (2 - 5%)
   - Uncontrolled diabetes
   - Resistant hypertension
   - Polycystic ovary syndrome
4. Osteoprosis at young age (3%) especially with rib fracture
   - Premenopausal women
   - Men < 65 years
5. Incidental adrenal mass > 2 cm (9%)
6. Hypogonadotropic hypogonadism with increased lanugo hair and papular acne

Diagnosis

Cushing's syndrome should be differentiated from pseudo-Cushing's syndrome[4]. Pseudo-Cushing's is defined as a state in which some or all the clinical features that resemble Cushing's syndrome and evidence of hypercortisolism are present on screening test, but disappear after resolution of underlying condition. The most common causes of pseudo-Cushing's syndrome include obesity, chronic alcoholism, depression and acute illness of any type. The tests used to differentiate between these two clinical disorders are insulin tolerance test, loperamide (16 mg orally) test and combined dexamethasone-CRH test. Out of these three tests, combined dexamethasone-CRH test has sensitivity and specificity of 99% and 96% respectively. The test involves administration of 0.5mg oral dexamethasone every 6 hour for 2 days, ending 2 hours before administration of ovine CRH (1mg/kg) intravenously. The plasma cortisol value 15 minutes after CRH less than 40 nmol/l (1.4 mg/dL) excludes the diagnosis of Cushing's syndrome[19].

The diagnosis of Cushing's syndrome involves two steps. First, establishing that the patient is having hypercortisolaemia; and second, establishing the cause of this hypercortisolaemia. No single test is perfect and each has a different sensitivity and specificity. The tests used to establish a diagnosis of Cushing's syndrome include circadian rhythm of cortisol, urinary free cortisol (UFC), overnight and low-dose dexamethasone suppression test (ONDST and LDDST)[20,21]. In normal subjects, plasma cortisol levels are highest in the morning and reach a nadir (< 50 nmol/L) at about midnight. This circadian rhythm is lost in patients with Cushing's syndrome. The midnight cortisol > 200 nmol/L indicates Cushing's syndrome with sensitivity of 94% and specificity of 100%[22,23]. Since more than 90% of the plasma cortisol is protein bound, the results of conventional assay are affected by drugs or conditions that alter cortisol binding globulin (CBG). Midnight salivary cortisol represents free cortisol and is an alternative in such cases. It has a sensitivity of 93% and specificity of 100%. The normal value of salivary cortisol is 4.3 nmol/L, while patients with Cushing's syndrome had >8.6 nmol/L[24]. Patients with intermediate values should have a repeat measurement or should undergo UFC or LDDST. UFC values of more than four times the upper limit of normal are rare except in Cushing's syndrome. UFC has a sensitivity and specificity of 95 - 100% and 90 - 95% respectively. The overnight dexamethasone suppression test with 1 mg of dexamethasone given at 11pm in the night with 08 00 hr cortisol value of < 140 nmol/l has a sensitivity of 95% and specificity of 88%. The sensitivity of this test can be improved to 98 - 100% by reducing post-dexamethasone cortisol value to less than 50 nmol/

L[25]. The 48-hour LDDST (0.5 mg dexamethasone every 6 hrs) with post-LDDST cortisol level of less than 50 nmol/L has a sensitivity of 98 - 100% and a specificity of 97 - 100%[26]. However, some 3% - 8% of patients especially those with cyclic Cushing's disease retain sensitivity to dexamethasone and show suppression of serum cortisol to less than 50 nmol/L on either test. Thus, if clinical suspicion remains high, repeated testing is indicated with future follow-up.

Having established the diagnosis of Cushing's syndrome, the next step involves finding out the cause of Cushing's syndrome. Measurement of 9 am ACTH differentiates between ACTH-dependent Cushing's syndrome from ACTH-independent causes. ACTH > 20 pg/ml suggests ACTH-dependent causes, while < 10 pg/ml suggests ACTH-independent aetiologies. Patients with values between 10 - 20 pg/ml should be subjected to CRH stimulation test (1 mg/kg IV). Post-CRH stimulation ACTH of more than 20 pg/ml suggests ACTH-dependent Cushing's syndrome[27]. The value of high-dose dexamethasone suppression test (HDDST) in discriminating various aetiologies is questioned by many studies[28]. There is a little difference between results of HDDST in patients with Cushing's disease and those with ectopic ACTH syndrome. Furthermore, if suppression of serum cortisol by more than 30% occurs with LDDST, there is no further advantage of using HDDST (Table III).

Table III: Sensitivity and specificity of various biochemical tests used in making a diagnosis of Cushing's syndrome.

Biochemical test	Sensitivity	Specificity
Loss of ciracadian rhythm with midnight cortisol > 200 nmol/l	94%	100%
Overnight dexamethasone suppression test (ONDST) with a cutoff ≤ 50 nmol/l	98 - 100%	88%
Low dose dexamethasone suppression test (LDDST)	98 - 100%	97 - 100%
Late night salivary cortisol	93%	100%
High dose dexamethasone suppression test (HDDST)		
● > 90% suppression of basal 08 00 hr plasma cortisol	67 - 70%	100%
● 8 mg single dose	92%	100%
HDDST + CRH	90%	90%
Inferior petrosal sinus sampling (IPSS)	95 - 99%	100%

The next step involves MRI of sella if patient is suspected having pituitary-dependent Cushing's syndrome, or CT scan of the chest and abdomen to find out ectopic source of Cushing's syndrome, or for adrenal causes of Cushing's syndrome. A major drawback of pituitary imaging is that up to 40% of cases with biochemically proven Cushing's disease have normal pituitary MRI scan and a tumour of less than 5 mm on imaging has a poor correlation with aetiological diagnosis[29]. In these cases inferior petrosal sinus sampling (IPSS) remains the gold standard. A basal central: peripheral ratio of more than 2:1 or 3:1 after CRH stimulation has a sensitivity of 95 - 99% and specificity of 100% in establishing a diagnosis of Cushing's disease[30]. The algorithm for the diagnosis of Cushing's syndrome is shown in Figure 1.

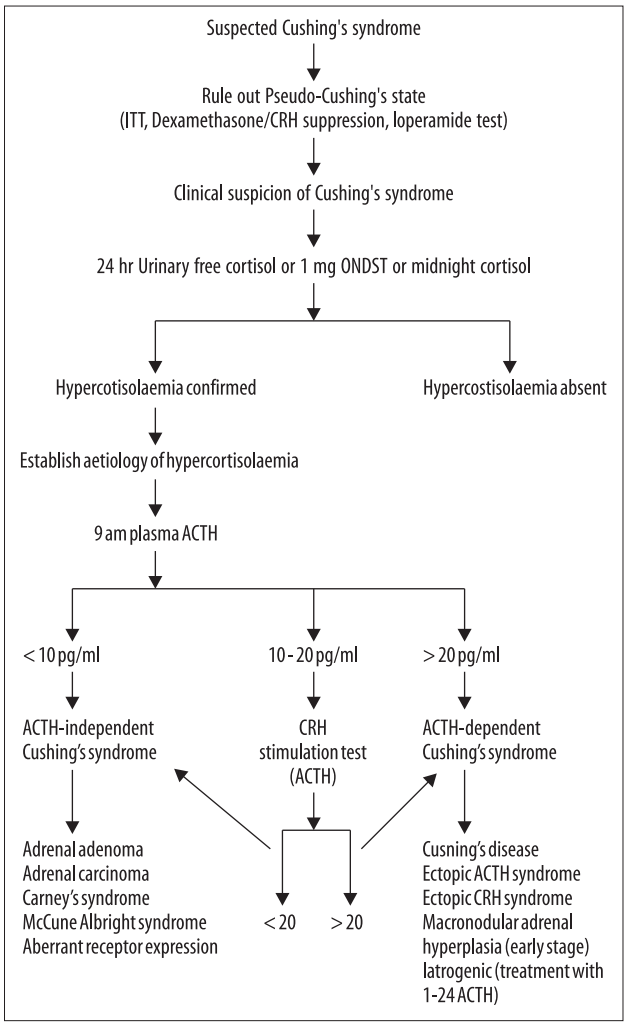

Fig. 1: *Algorithm for the diagnosis of Cushing's syndrome.*

Treatment

The patients with marked hypercortisolaemia, i.e., plasma cortisol > 1,200 nmol/l are especially at risk of severe infections like *Pneumocystis carinii*, aspergillosis, candidiasis, nocardiosis, cryptococcosis, and visceral perforation[31]. The approach of many centres to use routine pre-operative medical adrenal blockade with ketoconazole to achieve eucortisolaemia for 4 - 6 weeks

before surgery to restore metabolic and catabolic effects of hypercortisolaemia is empirical[32]. There is no randomised trial to support this approach. Since Cushing's syndrome is a prothrombotic state, anticoagulant prophylaxis should be given to all the patient's pre-operatively[33].

The treatment of Cushing's disease is trans-sphenoidal surgery by an experienced neurosurgeon. Cure rate for microadenoma is 80 - 90% while it is only 50% for macroadenoma[34]. The recurrence rate for established cure after successful pituitary surgery is 2% but this is higher in children (up to 40%). The undetectable cortisol within 24 - 72 hours after the surgery establishes the cure. Patients who are hypocortisolic (undetectable plasma cortisol) post-operatively should be given 10 mg/m^2 of hydrocortisone in three divided doses. Patients should be educated about the need to double the oral dose for nausea, diarrhoea, and fever, and should take intravenous glucocorticoid during severe medical stress. Recovery of HPA axis is monitored by measuring 9 am cortisol 24-hr after omission of hydrocortisone replacement. Because recovery of HPA axis rarely occurs before 3 - 6 months, it is cost-effective to do an initial testing at 6-months post-operatively. If the patient continues to show subnormal cortisol response up to 2 years after the surgery, then patient needs lifelong glucocorticoid replacement therapy[35]. The adrenal adenoma should be removed by unilateral adrenalectomy with 100% cure rate[36]. Adenoma of less than 6 cm size can be removed by laparoscopic adrenalectomy[37]. Patient needs to be given hydrocortisone replacement therapy as trans-sphenoidal surgery. After unilateral adrenalectomy, the time to recovery of HPA axis may be as short as 3 months to as long as 2 years. Adrenal carcinoma has a poor prognosis as majority has metastasis at the time of diagnosis. Furthermore, adrenocortical carcinoma responds poorly to radiotherapy and chemotherapy.

Pituitary irradiation – both conventional or gamma knife – has been recommended to treat Cushing's disease when surgery fails, except in children where pituitary irradiation is more effective and can be used as primary treatment modality for Cushing's disease[38]. The gamma knife has a remission rate of 76% with normalisation of cortisol value within 12 - 36 months.

Bilateral adrenalectomy provides rapid resolution of hypercortisolic state in any ACTH-dependent hypercortisolaemia; however, the patient needs to take lifelong glucocorticoid and mineralocorticoid replacement therapy[39]. A major concern after bilateral adrenalectomy in patients with Cushing's disease is the development of Nelson's syndrome – a locally aggressive pituitary tumour that secretes high concentrations of corticotrophin, resulting in pigmentation[40]. The exact pathogenesis of Nelson's syndrome is not clear. It is believed that the tumour results either from the lack of cortisol feedback after adrenalectomy, or because of progression of previously undetected corticotrophe tumours that were programmed to behave in an aggressive manner from the beginning. The treatment of Nelson's syndrome involves trans-sphenoidal pituitary surgery or radiotherapy. Some clinicians advocate use of prophylactic pituitary radiotherapy at the time of bilateral adrenalectomy to reduce the risk of this syndrome, but others have not confirmed this finding.

In Cushing's disease, patients who fail to achieve a cure with TSS and or radiotherapy, or who cannot opt for adrenalectomy, medical therapy can be used to ameliorate hypercortisolism[41]. Overall, medical treatment may be useful in up to one-third of Cushing's disease patients. These agents fall under three major categories based on their mechanism of action, which include inhibitors of steroidogenesis, modulators of ACTH release, and cortisol receptor antagonists. Pharmacological management of Cushing's disease is usually directed at decreasing adrenal steroid production by ketoconazole, mitotane, metapyrone, aminogluthetimide[42].

Ketconazole is the best tolerated drug available for control of hypercortisolism[43]. It is an imidazole derivative and inhibits 11-β hydroxylase, 17-hydroxylase and CYP 17 - 20 lyase enzyme activity. It also interferes with ACTH-induced cAMP production and is a weak competitor for glucocorticoid receptor. It is used in the dose of 200 - 400 mg twice or thrice daily and is effective in 30 - 50% of cases. It has been used safely up to 83 months in various studies[44]. The oral absorption is facilitated by gastric acidity so it should be given after the meals, and concomitant use of antacids, proton pump blockers should be avoided. It can be used safely in children and in pregnant women. However, it is associated with hepatotoxicity in 5 - 10% of cases and causes gynaecomastia, oligozoospermia, and decreased libido in men.

Mitotane is a O,P′-DDT derivative and inhibits cholesterol side chain, 11-β hydroxylase and 3β-hydroxysteroid dehydrogenase enzyme[45]. It spares aldosterone metabolism. It is effective in up to 80% of patients and its effect persists as long as 2 years even after stopping the drug due to its lipophilic properties. Its effect is seen at a dose of 4 - 12 gm once a day that achieves a plasma concentration of 14 - 20 µg/ml. However, a majority of patients develop neurological (drowsiness, gait disturbances, vertigo, and problem with language) and gastrointestinal (nausea, vomiting, and diarrhoea) side effects at this dose. These side effects can be avoided by beginning at a dose of 0.5 - 1 g/day, gradually increasing

at 1 - 4 week interval and by administering it with meals or at bedtime with milk. Other adverse effects include fatigue (due to decreased cortisol), gynaecomastia, hypouricaemia, hypercholesterolaemia, elevated liver enzymes, and abnormal platelet functions. Since mitotane increases cortisol binding globulin, sex hormone binding globulin and thyroxine binding globulin, total serum cortisol cannot be used to monitor therapy, and urinary free cortisol and or/ACTH should be used for this purpose. Also, it increases the metabolic clearance of exogenously administered steroid, so the replacement doses of glucocorticoid must be increased by approximately one-third.

In severely ill patient who are unresponsive or unable to ingest an oral drug, etomidate (an imidazole derivative) can be used intravenously at a dose of 1.2 - 2.5 mg/hr to control hypercortisolaemia[46]. It has potent inhibitory effect on 11-β hydroxylase and less pronounced effect on 17-hydroxylase, 17-20 lyase and side chain cleavage enzyme activity. It also inhibits adrenocortical cell proliferation and expression of ACTH receptor. However, its use is limited because of its need to be given intravenously, and sedation which it causes even at therapeutic doses. After its use, adrenal insufficiency occurs invariably, therefore replacement with hydrocortisone or dexamethasone is mandatory.

Neuromodulatory compounds that affect CRH or ACTH synthesis or release include serotonin antagonists (cyproheptadine), dopamine agonists (bromocriptine and cabergoline), γ-aminobutyric acid reuptake inhibitor (sodium valporate) and somatostatin analogue (octreotide). All these compounds are used principally for Cushing's disease; however no large-scale placebo-controlled studies have been done with these compounds. A recent study demonstrated that dopamine receptors are expressed in neuroendocrine tumours associated with ectopic ACTH secretion causing Cushing's syndrome. Cabergoline treatment was found to be associated with normalisation of urinary cortisol in a subgroup (66.7%) of these patients. However, studies involving larger number of patients are mandatory to confirm the usefulness of dopamine agonist in ectopic ACTH syndrome[47-49].

Mifepristone (RU 486) is a competitive antagonist of glucocorticoid and progesterone receptors[50]. It is used in doses of 5 - 25 mg/kg or 400 - 800 mg/day. However, absence of peripheral marker of anti-glucocorticoid activity, long half-life, and difficulty in counteracting its anti-glucocorticoid activity limits the clinical use of this compound.

Newer medical treatment modalities include new multiligand somatosatin analogue SOM 230 (pasireotide), high-dose peroxisomal proliferator-activated receptor γ agonist rosiglitazone, retinoic acid, doxazosin[51].

SOM-230 (pariseotide) has high affinity for somatostatin receptor subtypes sst1, sst2, and sst5 (respectively 30, 5 and 40 times more than octreotide) and has been recently studied *in vitro*[52]. Basal and corticotrophin-releasing hormone induced ACTH release was inhibited and sensitivity of this treatment was not influenced by pre-treatment with dexamethasone. The inhibitory effect on basal ACTH was seen only after prolonged exposure, and is probably due to resistance to desensitisation and/or downregulation of endogenously expressed sst5 receptors. In a recent study, expression of somatostatin receptor 1, 2, 4 and 5 have been demonstrated in 13 patients with Cushing's disease and SOM 230 had been found to suppress cell proliferation and ACTH secretion in primary culture of human corticotrophe tumours significantly[53]. These results suggest that SOM-230 may have a role in medical treatment of pituitary-dependent Cushing's syndrome and multicentre clinical trials are underway to answer some of these questions.

Peroxisome proliferator-activated receptor expression is restricted and only colocalises with ACTH-secreting cells. There is abundant expression in ACTH-secreting adenomas. *In vitro* and in mice, plasma ACTH is significantly decreased by PPAR-γ ligands. As PPAR-γ ligands inhibit tumour cell growth in human breast cancer cells *in vitro* and in prostate cancer, it was postulated that it would have favourable effects on treating pituitary adenomas[54]. Rosiglitazone has been shown to induce G0/G1 cell-cycle arrest and apoptosis and suppress ACTH secretion in human and murine corticotrophe tumour cells. Unfortunately, rosiglitazone is unable to affect ACTH and cortisol secretion, at least in acute conditions, in patients with ACTH-secreting pituitary adenomas. In a recent study (10 patients that underwent unsuccessful TSS and four that were untreated), the administration of a single dose of rosiglitazone did not decrease ACTH/cortisol levels or blunt their response after corticotrophin releasing hormone injection[55]. In another study, seven patients with persistent Cushing's disease after failed pituitary TSS were treated with rosiglitazone at a dose of 8 mg/day[56]. Three of the cases showed a mild clinical improvement, moderate ACTH response and marked decrease in urinary free cortisol levels for 1 - 4 months after initiation of treatment. In tumours that were removed from patients treated with rosiglitazone, about 50% of cells maintained strong ACTH immunoreactivity. It is not clear why PPAR-γ agonists have a more pronounced effect on cortisol secretion than on ACTH secretion; some studies postulate that these agents have a direct effect on steroidogenic

enzymes and on antagonism of the actions of glucocorticoids on target organs. In a recent study involving six patients with Nelson's syndrome (bilateral adrenalectomy done for Cushing's syndrome), rosiglitazone at a dose of 12 mg/day did not change circulating ACTH concenteration over 12-week study period despite demonstration of PPAR-γ receptor expression in tumour tissue[57]. However, the authors concluded that despite being a negative study the demonstration of PPAR-γ receptor over tumour tissue suggest that a higher dose or more potent agonist might prove useful in other patients.

Retinoic acid has been found to have a potent inhibitory effect on corticotrophe tumour growth, plasma ACTH and corticosterone secretion, and reversed Cushing's phenotypic characteristics in various animal models[58]. This effect seems to be mediated through inhibition of the transcriptional activity of AP-1 and the orphan nuclear receptors Nur77 and Nur1. Retinoic acid treatment resulted in reduced pro-opiomelanocortin transcription and ACTH production. ACTH inhibition was also observed in human pituitary ACTH-secreting tumour cells, but not in normal cells, being correlated with the expression of the orphan receptor COUP-TFI (found in normal corticotrophes, but absent in pituitary Cushing's tumours). These potential anti-secretory and anti-proliferative properties of this agent in Cushing's syndrome need to be investigated further.

α1-adrenergic receptor antagonists also represent a potential novel therapy for pituitary adenomas[59]. A study published in 2005 showed that doxazosin treatment inhibited proliferation of murine pituitary tumour cells and induced G0/G1 cell-cycle arrest. In mice with corticotrophe tumours, doxazosin administration decreased tumour growth and reduced plasma ACTH levels. The mechanism is still unclear, but these effects were not mediated via the α1-adrenergic receptors. The validity of these observations needs confirmation in clinical trials.

Following successful treatment, features of Cushing's syndrome disappear over a period of 2 - 12 months period[60]. Skin desquamation occurs shortly after surgery and weight loss, decrease in medication for blood pressure and diabetes occurs over the time, and some may have normal glucose tolerance. Osteopenia improves slowly over 2 years[61]; reproductive and sexual functions return to normal within 6 months. Vertebral fracture, aseptic necrosis are irreversible.

Thus, the diagnosis and treatment of Cushing's syndrome remains a challenging problem in clinical practice with rewarding results if done timely.

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REVIEW ARTICLE

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Post-prandial hyperglycaemia

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Abstract

Patients with type 2 diabetes may spend more than half the day in the post-meal state; most of these peaks are missed. Elevations in postmeal plasma glucose are due to the loss of first phase insulin secretion, decreased insulin sensitivity in peripheral tissues, and consequent decreased suppression of hepatic glucose output after meals due to insulin deficiency. Elevated/exaggerated post-meal response is directly responsible for endothelial dysfunction and the accompanying pro-atherogenic states. It is important to identify patients at risk of post-meal or excessive glycaemic excursions and to regularly monitor their PPG levels. Dietary interventions and pharmacologic therapies specifically targeted at post-meal plasma glucose help control the PPG levels.

Key words: type 2 diabetes, post-prandial (post-meal) hyperglycaemia.

Introduction

Diabetes is fast becoming a leading cause of death amongst the non-communicable diseases category not only in developed nations but also in many developing and newly industrialised nations. Poorly controlled diabetes is associated with the development of such complications as neuropathy, renal failure, vision loss, macrovascular diseases, and amputations. Macrovascular complications are the major cause of death in people with diabetes[1].

The developing economies of India and China, which account for about 37% of the world's total population put together now account for approximately half of the global diabetes burden[2]. This change is intimately linked to increase in caloric intake with increased sedentary activity patterns that have undergone gradual transformation for worse in these geographic areas. Traditional Asian Indian food habits are conventionally carbohydrate-rich – sometimes even as high as 80 per cent of the total caloric intake. The higher glucose load in the diets is responsible for an exaggerated prandial glycaemic response due to an increased glucosidase and incretin activity in the gut. This in turn leads to a higher lipaemic peak which has a direct epidemiological correlation with cardiovascular disease. Elevated/exaggerated post-meal response is seen in the pre-diabetes state which is directly responsible for endothelial dysfunction and the accompanying pro-atherogenic states. Patients with type 2 diabetes may spend more than half the day in the post-meal state; most of these peaks are missed as we are targeting a more fasting and glycosylated haemoglobin centric approach according to the American Diabetes Association (ADA) criteria. Post-meal responses are a direct reflection of the guts's ability to handle carbohydrate/nutrient load through the entero-insular/incretin axis and the glucosidases which reside in the brush border of the intestines. This is the reason medications directed towards incretin axis and the alpha-glucosidase inhibitors work relatively well in our population.

Why does a surge in post-meal hyperglycaemia occur?

A combination of genetic and environmental factors predispose patients to diabetes. These factors lead to impaired insulin secretion from pancreatic β-cells and insulin resistance in skeletal muscles, adipose tissue, and the liver. Insulin resistance in skeletal muscles and adipose tissue results in impaired glucose uptake and clearance, whereas insulin resistance in the liver results in the failure of insulin to suppress excessive hepatic glucose production. In people with normal glucose tolerance, plasma glucose generally does not rise more than 140 mg/dl in response to meals, and typically returns to pre-meal levels within two to three hours[3]. The World Health Organisation defines normal glucose tolerance as < 140 mg/dl two hours following ingestion of a 75 gm glucose load in the context of an oral glucose tolerance test. Even before diagnosis of clinical diabetes, these metabolic abnormalities are first evident as elevations in post-meal plasma glucose, due to the loss of first phase insulin secretion, decreased insulin sensitivity in peripheral tissues, and consequent decreased suppression of hepatic glucose output after meals due to insulin deficiency.

The combination of impaired insulin secretion and insulin resistance leads to impaired glucose tolerance (IGT; post-meal hyperglycaemia), impaired fasting glucose (IFG; fasting hyperglycaemia), and, eventually, to type 2 diabetes. Deficiencies in amylin, a pancreatic hormone co-

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secreted with insulin, and the incretin hormone glucagon-like peptide-1 (GLP-1), which stimulates glucose-dependent insulin secretion from pancreatic β-cells, suppresses glucose-dependent glucagon secretion from pancreatic α-cells, and reduces hepatic glucose production secondary to glucagon suppression. Day time suppression of post-meal excursion is lost first, followed by nocturnal deterioration of fasting sugars with worsening diabetes[4].

What factors are responsible for post-meal damage?

At the biochemical level, mechanisms implicated for hyperglycaemia-mediated tissue damage involve mitochondrial superoxide production. Oxidative stress has been implicated as the underlying cause of both the macrovascular and microvascular complications associated with type 2 diabetes. Current thinking proposes that hyperglycaemia, free fatty acids, and insulin resistance feed into oxidative stress, protein kinase-C (PKC) activation and advanced glycated endproduct receptor (RAGE) activation, leading to vasoconstriction, inflammation, and thrombosis.

Proposed pathophysiologic mechanisms of tissue damage due to post-meal hyperglycaemia

Hyperglycaemia-induced mitochondrial production leads to:-

- Increased flux in polyol pathway
- Increased intracellular formation of advanced glycation end-products
- Protein kinase C activation
- Increased flux through hexosamine pathway

Recent studies have suggested that acute glucose fluctuations lead to an increased urinary excretion of 8-iso-prostaglandin F2a, a marker of oxidative stress. Further studies are underway to validate these interesting findings[5].

Why should we target post-meal glucose?

Until recently, the predominant focus of therapy has been on lowering HbA1c levels, with a strong emphasis on fasting plasma glucose. Although control of fasting hyperglycaemia is necessary, it is usually insufficient to obtain optimal glycaemic control.

Post-meal hyperglycaemia has been identified as an independent risk factor for cardiovascular disease in patients with or without diagnosed diabetes, implying that post-meal measurements may be a better risk predictor than is FPG or HbA1c alone. Post-meal, but not FPG, is a significant predictor of subsequent myocardial infarction (MI) and death in patients with newly diagnosed type 2 diabetes. In addition, reductions in carotid intima-media thickness (CIMT) have been linked to changes in post-meal but not fasting hyperglycaemia or HbA1c, and post-meal has been associated with the development of complications like diabetic nephropathy and retinopathy. Acute hyperglycaemia in response to oral glucose loading in people with normal glucose tolerance, IGT, or type 2 diabetes, rapidly suppressed endothelium dependent vasodilation and impaired endothelial nitric oxide release[6].

Study	Key findings
DECODE[7]	2-hr blood glucose levels following 75 gm OGTT better predictor of all cause and cardiovascular deaths than FBG
Chicago Heart Association[8]	Increased risk of CVD mortality with higher PPG levels (after 50 gm OGTT)
Temelkova-Kurktschiev *et al*[9]	2-hr blood glucose levels and spikes more strongly associated with CIMT than FPG or HbA1c
Diabetes intervention study	Post-meal, but not FBG, significant risk factor for MI and mortality
Campanian post-prandial hyperglycaemia study	Reduction of post-meal, but not FPG, associated with reductions in CIMT

DECODE = Diabetes epidemiology collaborative analysis of diagnostic criteria in Europe; OGTT = Oral glucose tolerance test; FBG = Fasting blood glucose; CVD = Cardiovascular disease; CIMT = Carotid intima media thickness; HbA1c = Glycosylated haemoglobin; MI = Myocardial infarction.

Apart from the metabolic perturbations, post-meal hyperglycaemia has also been implicated in the development of pancreatic cancer. A large, prospective cohort study found a strong correlation between pancreatic cancer mortality and post-load plasma glucose levels[10]. The relative risk for developing pancreatic cancer was 2.15 in people with post-load plasma glucose levels of > 200 mg/dl compared with people who maintained post-load plasma glucose < 121 mg/dl. This association was stronger for men than women[11].

Post-meal hyperglycaemia is associated with impaired cognitive function in elderly people with type 2 diabetes[12]. Even in younger individuals with diabetes, consistent elevation of post-meal glycaemia is associated with significant levels of depression[13,14].

How to recognise post-meal hyperglycaemia?

It is important to identify patients at risk of post-meal or excessive glycaemic excursions and to regularly monitor their PPG levels. Excessive post-meal glycaemic excursions are common in patients with type 2 diabetes, even those

considered well controlled according to HbA1c values and FPG levels. Post-meal is one of the earliest defects in diabetes and is the predominant contributor to HbA1c at values below 8.4%, which is the common HbA1c value at presentation in our clinical scenario[15].

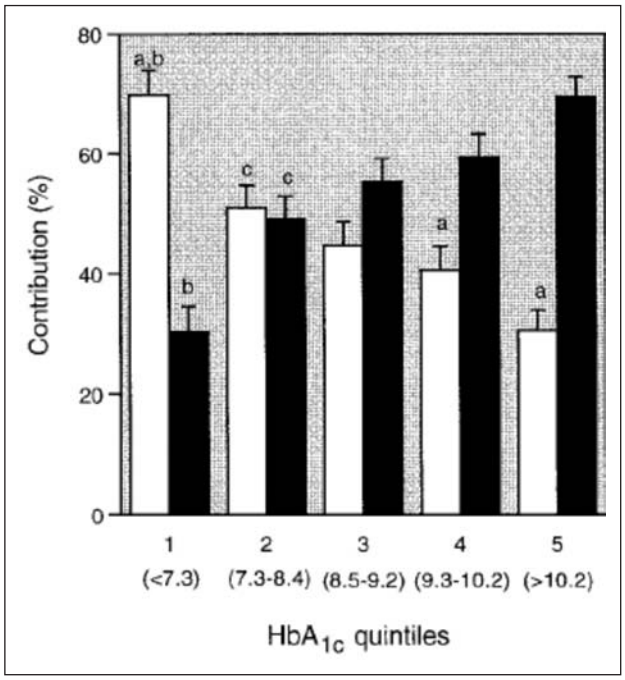

Fig. 1: *Relative contributions of post-prandial (white bars) and fasting (black bars) hyperglycaemia (%) to the overall diurnal hyperglycaemia over quintiles of HbA1c.*

HbA1c is an integrated measure of glycaemic exposure over the previous 2 to 3 months[16]. Although post-meal may contribute more at lower HbA1c values, it is still not possible to use HbA1c to identify patients with post-meal glycaemic excursions or isolated post-meal, whereas appropriately timed Self Monitoring of Blood Glucose (SMBG) is ideal for detecting and monitoring post meal. Glucose profiles, in which patients monitor at different times throughout the day or over several days to determine representative diurnal glucose levels, can help detect post meal excursions (Fig. 1). Post-meal SMBG values are often the highest glucose readings of the day and may motivate patients to avoid problem foods, increase physical activity to manage hyperglycaemic excursions, or evaluate and adjust medications appropriately[17]. Continuous monitoring of blood glucose profile (Fig. 2) adds to identification of post-meal surges in apparently well controlled diabetics. It is not that expensive and involves the use of a sensor to measure blood glucose continuously over a period of 3 days which gives readings every 5 minutes. The data can then be downloaded on a computer and analysed to see where corrections in treatments are needed[18].

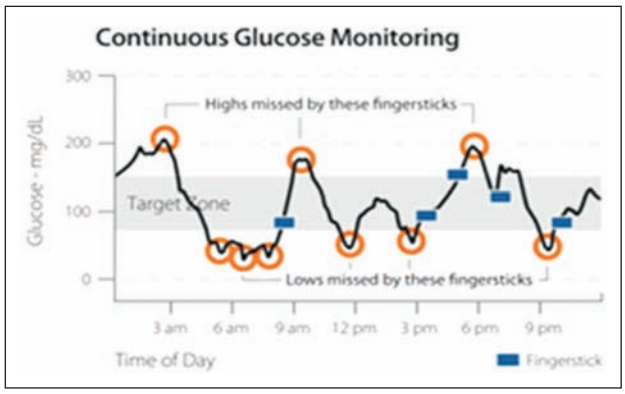

Fig. 2: *Continuous monitoring of blood glucose profile for identification of post-meal surges.*

Two other laboratory tests have been approved by the US Food and Drug Administration (FDA) for the monitoring of glycaemia. These measures of short-term glucose exposure include fructosamine and 1,5-anhydroglucitol measures. Given their shorter half-life, these measures are likely to be a more accurate reflection of post-meal blood glucose values. In particular, 1,5-anhydroglucitol has been proposed as a useful adjunct to A1C measures in monitoring post-prandial hyperglycaemia. As blood glucose levels increase, even transiently, these levels change within 24 hours as a direct result of increased glucose excretion in the urine[19]. Several studies have demonstrated that this measure improves significantly as post-meal blood glucose control is improved. When combined with A1C testing, self-monitored blood glucose tests, as well as these newer measures, may allow more accurate prediction and control of post-meal blood glucose levels.

How to treat post-meal hyperglycaemia?

Dietary interventions

Diets with a low glycaemic index (GI) are beneficial in controlling post-meal plasma glucose. Some forms of carbohydrate may exacerbate post-meal glycaemia. Most modern starchy foods, including the ones mostly contributing towards daily diet, have a relatively high GI, including potatoes, white and brown bread, rice and breakfast cereals. Foods with a lower GI (e.g., legumes, pasta, and most fruits) contain starches and sugars that are more slowly digested and absorbed, or less glycaemic by nature (e.g., fructose, lactose). The use of GI can provide an additional benefit for diabetes control beyond that of carbohydrate counting. Observational studies in populations without diabetes suggest that diets with a high GI are independently associated with increased risk of type 2 diabetes, gestational diabetes, and cardiovascular disease[20]. Despite inconsistencies in the data, sufficient

positive findings suggest that nutritional plans based on the judicious use of the GI positively affect post-meal plasma glucose excursions and reduce cardiovascular risk factors.

Pharmacotherapy

Pharmacologic therapies which specifically target post-meal plasma glucose include α-glucosidase inhibitors, glinides (rapid-acting insulin secretagogues) and insulin (insulin analogues, biphasic [premixed] insulins, inhaled insulin, regular insulin), DPP IV inhibitors, and GLP-1 analogues and amylin analogues.

α-glucosidase inhibitors

α-glucosidase inhibitors (AGIs) work by delaying the absorption of carbohydrates from the gastrointestinal tract, thereby limiting post-meal plasma glucose excursions. They competitively inhibit the enzyme α-glucosidase located in the proximal small intestinal epithelium that breaks down disaccharides and more complex carbohydrates, thereby delaying intestinal carbohydrate absorption and attenuating post-meal plasma glucose excursions. Side effects include mainly the GI effects like abdominal cramps, bloating, and diarrhoea, which in majority of cases do resolve on continuation of the drug[21].

Glinides

Glinides have a mechanism of action similar to sulfonylureas, but have a much shorter metabolic half life. They stimulate a rapid but short-lived release of insulin from pancreatic β-cells that lasts one to two hours. When taken at meal times, these agents attenuate post-meal plasma glucose excursions and decrease the risk of hypoglycaemia during the late post-meal phase because less insulin is secreted several hours after the meal. They are especially useful in elderly diabetics with brittle diabetes or those with hypoglycaemias in conventional sulfonylureas[21].

Insulins

Rapid-acting and premix insulin analogues

Insulin analogues were developed to mimic the normal physiologic insulin response. Rapid-acting insulins have a rapid onset and peak activity and a short duration of action. They are again useful in elderly diabetics, critical care illness patients, and patients on feeds through enteral routes (RT/NJ/NG feeds).

Inhaled insulin

Inhaled insulin consists of human insulin inhalation powder, which is administered using an inhaler. The inhaled insulin preparation has an onset of action similar to rapid-acting insulin analogues and a duration of glucose-lowering activity comparable to subcutaneously administered regular human insulin. The trials have uptil now been consistently disappointing, but further trials using improved formulations are still underway. The doubtful increased risk of lung malignancies was one of the hindrances in its early inception.

Oral Insulin

Trials with oral insulins are underway. In India, Biocon Company is leading in this field. If the results are indeed sufficiently exciting, this will be a remarkable improvement in insulin delivery systems.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors work by inhibiting the DPP-4 enzyme that degrades GLP-1, thereby extending the active form of the hormone. This in turn stimulates glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and increases satiety. The side effect profile is pretty much benign, with only a few reported instances of serious side effects. Caution is recommended in patients with hypertriglyceridaemia, alcoholics, and those with gallstones. Those with a history of pancreatitis should not be prescribed these classes of medications[22,23].

Glucagon-like peptide-1 (GLP-1) derivatives

GLP-1 is an incretin hormone secreted from the gut that lowers glucose through its ability to stimulate insulin secretion, increase β-cell neogenesis, inhibit β-cell apoptosis, inhibit glucagon secretion, decelerate gastric emptying, and induce satiety. It is the only class of medication that controls glycaemia and at the same time helps to lose weight and also has extra-glycaemic effects (improvement in systolic blood pressure, lipids, and markers of inflammation). This side-effect profile is similar to DPP-4 inhibitors[22,23].

Amylin analogues

Human amylin is a 37-amino acid glucoregulatory peptide that is normally co-secreted by the β-cells with insulin. Synthetic amylin analogue restores the natural effects of amylin on glucose metabolism by decelerating gastric emptying, lowering plasma glucagon, and increasing satiety, thereby blunting post-meal glycaemic excursions[24].

Conclusions

There appears to be no glycaemic threshold for reduction of complications, lower the better with avoiding hypoglycaemia, the goal of diabetes therapy

should be to achieve glycaemic status as near to normal as safely possible in all three measures of currently recommended glycaemic measures, namely HbA1c, fasting pre-meal and post-meal plasma glucose. Regimens targetting both fasting and post-meal glycaemia are needed to achieve optimal glucose control. However, optimal glycaemic control cannot be achieved without adequate management of post-meal plasma glucose. Therefore, treatment of fasting and post-meal hyperglycaemia should be initiated simultaneously at any HbA1c level. Although cost will remain an important factor in determining appropriate treatments, especially in a country like ours, controlling glycaemia is ultimately much less expensive than treating the complications of diabetes.

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"Medicine is the art of timeliness."

– Ovid.

REVIEW ARTICLE

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Vitamin D deficiency: A new risk factor for cardiovascular disease

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Abstract

Vitamin D deficiency is emerging as a new risk factor for various cardio-vascular diseases (CVDs), specifically atherosclerotic vascular disease. A number of epidemiological studies have shown that vitamin D deficiency is prevalent among many populations cutting across all ethnicities and among all age groups. With the growing menace of the epidemic of CAD, emergence of another commonly prevalent risk factor for the same is a matter of concern. Although the link between vitamin D deficiency and CAD has been consistently proven, interventional trials with supplementation of vitamin D or calcium have been disappointing in terms of risk reduction. Further research in this direction is underway and is likely to improve our understanding, and open up newer avenues for reducing the risk of CAD.

Key words: Vitamin D, calcium supplementation, coronay artery disease.

Introduction

Vitamin D deficiency is emerging as a new risk factor for various cardiovascular diseases (CVDs), especially atherosclerotic vascular diseases. With growing urbanisation and adoption of a westernised lifestyle, the prevalence of both CVD and Vitamin D deficiency are increasing. Apart from its direct role in CVD, vitamin D has also been attributed to other metabolic diseases which also affect CV health. Although vitamin D has been linked to a wide variety of diseases starting from cancer to immunological conditions, the focus here will be on CVD. Emergence of this particular association has a special importance in the Indian context. With a billion plus population and the burgeoning number of patients with CVD, emergence of another risk factor – vitamin D deficiency – which is commonly prevalent, should raise concern.

Prevalence of vitamin D insufficiency

Vitamin D deficiency is prevalent in India and worldwide. Several studies have demonstrated low serum vitamin 25 (OH) D levels in populations across India[1]. In North India, 96% of neonates[2], 91% of healthy school girls[3], 78% of healthy hospital staff[4], and 84% of pregnant women[2] were found to have hypovitaminosis D. In South India, hypovitaminosis D is equally prevalent among different population groups[5]. Hypovitaminosis D is equally prevalent among rural and urban subjects but in some studies urban subjects are found to be more deficient. In one report by Malhotra *et al,* vitamin D deficiency was reported to be found among diverse population groups in different countries of South Asia[6]. Vitamin D inadequacy constitutes a largely unrecognised epidemic in many populations worldwide. It has been reported in healthy children, young adults, especially African Americans, and middle-aged and elderly adults. Typically, the prevalence of low 25 (OH) D levels (< 20 ng/mL [50 nmol/L]) is approximately 36% in otherwise healthy young adults aged 18 to 29 years, 49.42% in black women aged 15 to 49 years, 50.41% in outpatients aged 49 to 83 years, up to 57% in general medicine inpatients in the United States, and even higher in Europe (28% - 100% of healthy and 70% - 100% of hospitalised adults). Vitamin D inadequacy is particularly common among patients with osteoporosis[7]. A recent systematic review by Gaugris et al concluded that the prevalence of inadequate 25 (OH) D levels appears to be high in post-menopausal women and especially those with osteoporosis and a history of fracture[8]. The results of a recent cross-sectional, observational study conducted at 61 sites across North America showed that 52% of post-menopausal women receiving therapy for osteoporosis had 25 (OH) D levels of less than 30 ng/mL (75 nmol/L)[9]. The high prevalence of vitamin D inadequacy in that study was consistent across all age groups and North American geographic regions studied. The prevalence of very low serum 25 (OH) D levels (<12 ng/mL [30 nmol/L]) was 76% among patients with osteoporosis in another study. A global study of vitamin D status in post-menopausal women with osteoporosis showed that 24% had 25 (OH) D levels less than 10 ng/mL (25 nmol/L), with the highest prevalence reported in central and southern Europe[10]. A study of Asian adults in the United Kingdom showed that 82% had 25 (OH) D levels less than 12 ng/mL (30 nmol/L) during the summer season, with the proportion increasing to 94% during the winter months[11]. A study of 1,546 African American women in

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the United States, ranging in agefrom 15 to 49 years, showed that more than 40% had serum25 (OH) D levels less than 15 ng/mL (37 nmol/L)[12].

Vitamin D photobiochemistry, metabolism, and functions

UV-B irradiation of skin triggers photolysis of 7-dehydrocholesterol (provitamin D3) to previtamin D3 in the plasma membrane of human skin keratinocytes. Once formed in the skin, cell plasma membrane previtamin D3 is rapidly converted to vitamin D3 by the skin's temperature. Vitamin D3 from the skin and vitamin D from the diet undergo 2 sequential hydroxylations, first in the liver to 25 (OH) D and then in the kidney to its biologically active form, i.e., 1, 25- dihydroxyvitamin D (1, 25 [OH] 2D) (Figure 1). Excessive solar UV-B irradiation will not cause vitamin D intoxication because excess vitamin D3 and previtamin D3 are photolysed to biologically inactive photoproducts. Melanin skin pigmentation is an effective natural sunscreen, and increased skin pigment can greatly reduce UVB-mediated cutaneous synthesis of vitamin D3 by as much as 99%, similar to applying a sunscreen with a sun protection factor of 15. Keratinocytes are also capable of hydroxylating 25 (OH) D to produce 1, 25 (OH) 2D. The 1, 25 (OH) 2D (from keratinocyte or renal sources) may regulate keratinocyte differentiation, melanocyte apoptosis, and melanin production, and this may be another mechanism for regulating the cutaneous synthesis of vitamin D3 by negative feedback. The 1, 25 (OH) 2D ligand binds with high affinity to the vitamin D receptor (VDR) and triggers an increase in intestinal absorption of both calcium and phosphorus. In addition, vitamin D is involved in bone formation, resorption, and mineralisation, and in maintaining neuromuscular function (Figure 1). Circulating 1, 25 (OH) 2D reduces serum parathyroid hormone (PTH) levels directly by decreasing parathyroid gland activity and indirectly by increasing serum calcium. The 1, 25 (OH) 2D regulates bone metabolism in part by interacting with the VDR in osteoblasts to release biochemical signals, leading to formation of mature osteoclasts. The osteoclasts release collagenases and hydrochloric acid to dissolve the matrix and mineral, releasing calcium into the blood. When vitamin D levels are inadequate, calcium and phosphorus homoeostasis becomes impaired. Vitamin D is primarily responsible for regulating the efficiency of intestinal calcium absorption. In a low vitamin D state, the small intestine can absorb approximately 10% - 15% of dietary calcium. When vitamin D levels are adequate, intestinal absorption of dietary calcium more than doubles, rising to approximately 30% - 40%. Thus, when vitamin D levels (25 [OH] D) are low, calcium absorption is insufficient to satisfy the calcium requirements not only for bone health but also for most metabolic functions and neuromuscular activity. The body responds by increasing the production and release of PTH into the circulation (Figure 1). The increase in PTH restores calcium homoeostasis by increasing tubular reabsorption of calcium in the kidneys, increasing bone calcium mobilisation from the bone, and enhancing the production of 1, 25 (OH) 2D[13].

Assessment of vitamin D status

Serum 25 (OH) D is the major circulating metabolite of vitamin D and reflects vitamin D inputs from cutaneous synthesis and dietary intake. The serum 25 (OH) D level is the standard clinical measure of vitamin D status. Although 1, 25 (OH) 2D is the active form of vitamin D, it should not be measured to determine vitamin D status. It usually is normal or even elevated in patients with vitamin D deficiency. Testing of serum 25 (OH) D is most useful in patients who are at risk of vitamin D deficiency, including elderly patients, infirm patients, children and adults with increased skin pigmentation, patients with fat malabsorption syndromes, and patients with osteoporosis. This measurement is also useful for purposes of planning or monitoring vitamin D therapy. Clinical assays of 25 (OH) D include the Nichols Advantage Assay (chemilu-minescence protein-binding assay, the DiaSorin radioimmunoassay, and the benchmark high-performance liquid chromatography assays and liquid chromatography mass spectroscopy assays. The chemiluminescence protein-binding assay and the radioimmunoassay are most commonly used to determine patient vitamin D status. Recent reports have raised concerns about the degree of variability between assays and between laboratories, even when using the same assay. Although reliable and consistent evaluation of serum 25 (OH) D levels remains an issue, reliable laboratories currently exist, and efforts are in progress to improve and standardise assays to enhance accuracy and reproducibility at other laboratories. As noted previously, vitamin D plays a central role in calcium and phosphorus homoeostasis and skeletal health. Since impaired calcium metabolism due to low serum 25 (OH) D levels triggers secondary hyperparathyroidism, increased bone turnover, and progressive bone loss, the optimal range of circulating 25 (OH) D for skeletal health has been proposed as the range that reduces PTH levels to a minimum and calcium absorption is maximal. Several studies have shown that PTH levels plateau to a minimum steady-state level as serum 25 (OH) D levels approach and rise above approximately 30 ng/mL (75 nmol/L)[14].

Nonskeletal consequences of vitamin D deficiency

It has long been recognised that people who live at higher latitudes face an increased risk of many chronic diseases, including common cancers, multiple sclerosis, and hypertension[15]. As early as 1941, Apperly observed that people living at higher latitudes, e.g., Massachusetts and New Hampshire, had a higher risk of dying of the most common cancers than did people living in the South, e.g., Georgia and South Carolina[16]. In 1979, Rostand reported that people living at higher latitudes in both the United States and Europe were at higher risk of hypertension[17]. In the late 1980s and early 1990s, several investigators reported increased risks of dying of colon, prostate, and breast cancer in people living at higher latitudes in both the United States and Europe. Grant reported that 25% of the deaths due to breast cancer in women in Europe could be attributed to the women's lack of UVB from exposure to sunlight[18]. Both men and women are at higher risk of dying of cancer if they have minimum exposure to sunlight. In a retrospective study, Ahonen *et al* reported that men on average begin to develop prostate cancer by the age of 52 years, whereas men exposed to more sunlight throughout their lives did not begin developing prostate cancer until 3 - 5 years later[19].

Vitamin D metabolism and noncalcaemic functions

It has been known since long that vitamin D3 made in the skin or coming from the diet requires 2 obligate hydroxylations, first in the liver and then in the kidney, to create the active form of vitamin D, 1, 25 (OH) 2D (Figure 1). 1, 25 (OH) 2D interacts with its nuclear receptor in the intestine, bone, and kidney to regulate calcium and bone metabolism. Most tissues and cells in the body, including heart, stomach, pancreas, brain, skin, gonads, and activated T and B lymphocytes, have nuclear receptors for 1, 25 (OH) 2D, called vitamin D receptors. Thus, it is natural that 1, 25 (OH) 2D has a multitude of biologic effects that are noncalcaemic in nature. One of the most intriguing, important and unappreciated biologic functions of 1, 25 (OH) 2D is its ability to down-regulate hyperproliferative cell growth. Normal and cancer cells that have a vitamin D receptor often respond to 1, 25 (OH) 2D by decreasing their proliferation and enhancing their maturation. This was the rationale for using 1, 25 (OH) 2D3 and its analogs to treat the common hyperproliferative skin disorder psoriasis. Vitamin D receptors are present in activated T and B lymphocytes and in activated macrophages. The most common autoimmune diseases, including type 1 diabetes, rheumatoid arthritis, and multiple sclerosis, have all been successfully prevented in models using mice that were prone to these diseases if they received 1, 25 (OH) 2D3 early in life. In a recent observation by Hypponen *et al* found that children receiving 2,000 IU vitamin from age 1 year on was decreased their risk of getting type 1 diabetes by 80%[20]. Krause *et al* reported that hypertensive patients exposed to UVB radiation for 3 months had a 180% increase in circulating concentrations of 25 (OH) D and a 6 mm Hg decrease in their diastolic and systolic blood pressures – results similar to those expected if the patients had received a blood pressure medication[21]. A similar group of patients who were exposed to ultraviolet A radiation and whose circulating concentrations of 25 (OH) D did not increase continued to be hypertensive throughout the 3-month study. The exact mechanism by which UVB radiation returned the blood pressure to normal [presumably due to increased blood concentrations of 25 (OH) D] in these hypertensive adults is not well understood, but the observation by Li *et al*[22] sheds some light on the question. They observed in a mouse model that 1, 25 (OH) 2D is effective in down-regulating renin and angiotensin and thereby decreasing blood pressure.

Vitamin D and cardiovascular health

Although the best-characterised sequelae of vitamin D deficiency involve the musculoskeletal system, a growing body of evidence suggests that low levels of vitamin D may adversely affect the cardiovascular system. Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle, endothelium, and cardiomyocytes. In vitro, activated 1, 25-dihydroxyvitamin D (1, 25-OH D) directly suppresses renin gene expression, regulates the growth and proliferation of vascular smooth muscle cells and cardiomyocytes, and inhibits cytokine release from lymphocytes. Studies in knockout mice confirm that the absence of vitamin D receptor activation leads to tonic upregulation of the renin-angiotensin system, with the development of hypertension and left ventricular hypertrophy. Clinical studies have reported cross-sectional associations between lower vitamin D levels and plasma renin activity, blood pressure, coronary artery calcification, and prevalent cardiovascular disease. Additionally, ecological studies have reported higher rates of coronary heart disease and hypertension with increasing distance from the equator, a phenomenon that has been attributed to the higher prevalence of vitamin D deficiency in regions with less exposure to sunlight. The possibility of a causal link between vitamin D deficiencyand cardiovascular disease is supported by biological plausibility, the demonstration of a temporal association, and the finding of a dose response between

25-OH D deficiency and risk. These data raise the possibility that treatment of vitamin D deficiency, via supplementation or lifestyle measures, could reduce cardiovascular risk. However, treatment strategies suggested by observational data are not always borne out by randomised trials, as evidenced by studies of hormone replacement therapy and B vitamins for homocysteine lowering. Problems related to the use of observational data include indication bias, confounding, and reverse causation. In a large observational study by Wang *et al* sponsored by the NIH, where they employed direct measurement of 25 hydroxy vitamin D, they concluded that moderate-to-severe vitamin D deficiency is a risk factor for developing cardiovascular disease.

Among different spectrum of cardiovascular diseases linked to vitamin D deficiency, CAD is the most extensively studied. A Danish study examined 25-hydroxyvitamin D (25 [OH] D) levels measured in 128 patients admitted to the hospital with ischaemic heart disease (75 with angina pectoris and 53 with acute MI) and 409 control subjects and found that 25 (OH) D levels were significantly lower in those with angina (23.5 ng/ or MI (24.0 ng/mL) than in controls (28.8 ng/mL)(23). In a New Zealand case control study, 3 of 179 patients with MI, cases had a lower mean 25 (OH) D level (P = .02), which was more pronounced in the winter-spring period than in the summer-autumn period. The relative risk (RR) of MI decreased across increasing quartiles of 25 (OH) D[24]. Multivariate analyses of major CVD risk factors did not appreciably alter the results. A small, nested, case control study of MI based in the Tromso Heart Study (northern Norway) with only 30 cases and 60 matched controls found a slightly nonsignificant lower 25 (OH) D level in cases (23.6 ng/mL) compared with controls (25.4 ng/mL)[25]. Another prospective study by Giovannucci, funded by the National Cancer Institute and the National Heart, Lung, and Blood Institute, vitamin D deficiency was found to be an independent risk factor for development of AMI after adjusting for all known CAD risk factors. In this cohort study, men with circulating 25 (OH) D levels of at least 30 ng/mL had approximately half the risk of AMI, independent of other CVD factors[26].

Potential mechanisms

Several mechanisms may explain the link between vitamin D deficiency and cardiovascular disease. First, experimental studies indicate that 1, 25 (OH) D participates in the regulation of renin-angiotensin axis by directly suppressing renin gene expression. Renin over-expression can be produced in wild-type mice by pharmacological inhibition of vitamin D synthesis. Second, vascular smooth muscle cells and endothelial cells express receptors for vitamin D and have the ability to convert circulating 25 (OH) D to 1, 25 (OH) D. Putative vascular effects of vitamin D are wide-ranging and include modulation of smooth muscle cell proliferation, inflammation, and thrombosis. Interestingly, transgenic rats constitutively expressing vitamin D-24-hydroxlyase, the enzyme that catalyzes the breakdown of 1 to 25 (OH) D, develop substantial atherosclerosis. Third, vitamin D deficiency triggers secondary hyperparathyroidism. Parathyroid hormone (PTH) promotes myocyte hypertrophy and vascular remodelling. Other studies suggest that PTH has a pro-inflammatory effect, stimulating the release of cytokines by vascular smooth muscle cells. Hypertension plays a key role in the development of left ventricular hypertrophy and vascular remodelling. Because vitamin D deficiency may also influence cardiac and vascular remodelling, hypertension could magnify the adverse effects of vitamin D deficiency on the cardiovascular system. Also, experimental and clinical data suggest that vitamin D deficiency directly promotes the development of hypertension, which provides another potential mechanism linking vitamin D deficiency, hypertension, and cardiovascular risk. Calcification is a common feature of atherosclerosis, and nearly all angiographically significant lesions are calcified. Calcification of coronary arteries has been associated with increased risk of MI and poorer 5-year survival. Atherosclerotic calcification is a process regulated in ways similar to skeletal osteogenesis. A significant association exists between osteoporosis and vascular calcification, suggesting that osteoregulatory mechanisms related to bone development may affect calcification in the vasculature. Levels of 1, 25-dihydroxyvitamin D have been shown to be inversely associated with vascular calcification, suggesting that vitamin D may affect MI risk through its effects on vascular calcification. Other mechanisms could account for or contribute to the association between 25 (OH) D and MI risk. Vitamin D deficiency, possibly combined with low calcium intake, has been associated with impaired fasting glucose and possibly risk of type 2 diabetes mellitus, risk factors for CVD.

In an excellent review published in the *Annals of Internal Medicine* by Pittas *et al*, the authors analysed different studies conducted on the role of vitamin D on different cardiometabolic outcomes and the effect vitamin D supplementation on them. They identified seven longitudinal studies, analysing vitamin D status and cardiovascular end-points including 43,527 participants who were followed from 5 to 27 years for incident cardiovascular disease. Cardiovascular end-points included myocardial infarction, cardiovascular related death, a composite cardiovascular end-point, and stroke. All studies measured 25 (OH) D concentration, and all

reported multivariate adjusted results. Overall, 5 of the 9 analyses found that lower 25 (OH) D concentration was associated with increased risk for incident cardiovascular disease.The Framingham Offspring Study found the association between lower 25 (OH) D concentration and increased risk for overall cardiovascular events to be nonlinear and the association was statistically significant only among participants with hypertension at baseline. The authors concluded that although cross-sectional studies have reported consistent associations between lower 25 (OH) D concentration or vitamin D intake and prevalent cardiometabolic outcomes in the longitudinal observational studies, lower 25 (OH) D concentration or vitamin D intake was associated with increased risk for incident hypertension and possibly cardiovascular disease, but the strengths of these associations were attenuated compared with those from cross-sectional studies[27].

Among the studies that evaluated fatal cardiovascular events, 2 of 3 found statistically significant associations that favoured higher vitamin D concentration for all fatal cardiovascular events (cardiac or stroke), 2 found similar significant associations with fatal stroke, and 1 found no significant association with fatal cardiac events. Of the 2 studies that evaluated myocardial infarction, only the analysis in the men-only Health Professionals Follow-up Study found a significant association between lower 25 (OH) D concentration and increased risk. The authors did not perform a meta-analysis because of the heterogeneity of outcomes[27].

Although data linking vitamin D deficiency and cardiovascular disease is consistent, the exact threshold at which risk for cardiovascular disease may increase is unclear. Relatively high levels of 25 (OH) D (> 30ng/mL) are required to maintain normal PTH levels, but optimal levels for cardiovascular protection may differ from those for bone metabolism or normal PTH physiology. Many studies report increased cardiovascular risk at 25 (OH) D levels well below 30 ng/mL. In the Framingham Offspring Study the mean 25 (OH) D concentration was 19.7 ng/mL. The overall prevalence of 25 (OH) D 15 ng/mL was 28%, with 9% having 25 (OH) D 10 ng/mL. The age- and sex-adjusted 5-year rate of cardiovascular disease was approximately twice as high in those with 25 (OH) D 15 ng/mL as in those with 25 (OH) D 15 ng/mL. The highest rate of cardiovascular disease was observed in those with hypertension and vitamin D deficiency. Although the study was reported to have inadequate statistical power to evaluate the effect of milder degrees of vitamin D deficiency (15 to 30 ng/mL), given the low proportion of individuals in the cohort with levels < 30 ng/mL (10%), an increased cardiovascular risk associated with decreased 25-OH D levels in analyses in which the reference group included individuals with "mild" deficiency was observed.

Role of vitamin D and calcium supplementation

With a growing evidence base implicating the role of vitamin D deficiency in cardiovascular diseases, correction of hypovitaminosis D and calcium supplementation should be the next logical step, because they attempt to address the pathophysiological anomaly involved in causation cardiovascular diseases. Unfortunately, data regarding the effect of these measures to prevent cardiovascular diseases have not been as consistent.

In a sytematic review of the role of vitamin D and calcium supplementation in prevention of cardiovascular events by Lu Wang *et al* published in the *Annals of Internal Medicine*[28], prospective studies of dialysis patients and a single cohort study involving a general population showed consistent reductions in CVD mortality among those who received vitamin D supplements. Randomised trials reported a slight but statistically nonsignificant reduction in CVD risk with vitamin D supplementation at moderate-to-high doses. In contrast, both prospective studies and randomised trials showed no apparent effect of calcium supplementation, with or without vitamin D, on the risk for CVD. A consistently strong inverse association between active vitamin D use and CVD mortality among patients receiving dialysis suggests a potential cardioprotective effect of vitamin D. However, the generalisation and applicability of such findings to broader populations warrants more study. Women's Health Initiative is the largest trial of vitamin D supplementation to date and has shown no effect of vitamin D plus calcium supplementation on CVD event risk. Notably, the vitamin D dosage of 400 IU/d used in the Women's Health Initiative increased median plasma 25-hydroxyvitamin D levels from 42.3 nmol/L to only 54.1 nmol/L. Extrapolating these data to achieve 25-hydroxyvitamin D levels above 75 nmol/L, the recommended level for several health outcomes, would require supplementation of at least 1,000 IU/d to determine whether improvements in vitamin D status may prevent CVD. These findings indicate that a protective effect of vitamin D supplementation on CVD is possible, but that a moderate-to-high dosage may be needed. Null findings in 4 large-scale prospective studies of initially healthy participants suggest that calcium supplements are unlikely to confer a major effect on CVD risk. Secondary analyses in 4 randomised trials also have not demonstrated a clear effect of calcium supplementation on CVD risk. A recent study by Bolland and co-workers raised concerns about a possible adverse effect of calcium

supplements on the risk for MI. In conclusion, evidence from prospective observational studies and randomised, controlled trials suggests that vitamin D supplementation at moderate-to-high doses may have beneficial effects on reducing the risk for CVD, whereas calcium supplementation seems to have no apparent effect on CVD risk[28].

One explanation of the inconsistencies in the intervention trials may lie in the fallacy of the vitamin D-cardiovascular risk hypothesis itself. Several possible reasons may explain the lack of apparent concordance among the cross-sectional, longitudinal observational, and randomised studies. Several factors may confound the inverse association between vitamin D status and cardiometabolic outcomes. First, vitamin D status is an excellent marker of good health, including positive associations with young age, normal body weight, and a healthy lifestyle, and negative associations with smoking, parental history of myocardial infarction, and alcohol intake. Second, lower vitamin D status may reflect chronic nonspecific illness. Therefore, the inverse association seen in cross-sectional studies may be due to reverse causation. Third, additional components in foods rich in vitamin D (such as fish or fortified dairy products) may directly affect cardiometabolic disease or, alternatively, foods rich in vitamin D may replace other foods that increase risk for cardiometabolic disease (for example, fortified milk may replace sweetened drinks). Finally, observational studies have used single measurements of serum or plasma 25 (OH) D concentration as a proxy for vitamin D status, even though this may not reflect long-term vitamin D status.

Conclusion

Despite these inconsistencies, data from trials involving haemodialysis patients and those where potential bias of immobility and lack of exposure to sunlight was eliminated by including mobile subjects like in that of Framingham Offspring Study, a positive association between vitamin D deficiency and cardiovascular diseases seems to be true and worth exploring further. Awaiting further trial data especially on the role of vitamin D supplementation, vitamin D health can safely be added to a growing list of modifiable risk factors, and achieving an optimal vitamin D store whether by the way of supplementation or by maintaining a healthy lifestyle and a good diet seems plausible and without any added cost.

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CASE REPORT

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Hepatitis E virus infection as a cause of acute hepatic failure in a patient of Wilson's disease

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Abstract

Wilson's disease may present as acute hepatic failure and may be missed as a differential diagnosis if there is no previous or family history. An acute insult like viral hepatitis may trigger Wilson's disease and may even progress to fulminant hepatic failure with grave prognosis. HAV and HEV infection have been shown to cause severe illness in patients with established chronic liver disease. This case suggests that viral infection may play a role in acute decompensation in some patients of Wilson's disease.

Key words: Fulminant Wilson's disease, hepatitis E, haemolysis.

Introduction

Wilson's disease has a broad spectrum of presentation such as acute liver failure, acute hepatitis, chronic hepatitis, and cirrhosis. Initial clinical symptoms of the disease may be non-specific and may go unrecognised without positive family history.

It has been postulated that an acute insult damages the hepatocytes which release free copper in toxic concentrations which in turn damage cell membranes – both directly and by free radical damage. Therefore, sometimes a hepatic injury other than Wilson's disease itself may primarily trigger the Wilson's disease [1].

This case report is a presentation of acute liver failure in a patient with biochemical evidence of Wilson's disease complicated by hepatitis E infection.

Case report

A 25-year-old male, unmarried patient, presented to us with jaundice, abdominal pain, vomiting, fatigue for 2½ months, and a disturbed sleep pattern for the last 7 days. There was no history of fever or bleeding manifestations.

There was no previous history of any liver disease. Family history was negative for any metabolic or inherited liver disease. Physical examination revealed icterus, hepatosplenomegaly, and flapping tremors were present. Stigmata of chronic liver disease were absent.

Laboratory investigations revealed: Hb – 9.3 gm/dl; TLC – 13,600/mm^3; polymorphs - 80%; lymphocytes – 16%; platelet count – 300,000/mm^3; reticulocyte count – 6%. Peripheral blood smear showed few histiocytes.

Serum bilirubin was 52 mg/dl: direct – 26 mg/dl; indirect – 25.8 mg/dl; SGOT – 65 IU/L; SGPT – 36 IU/L; ALP – 786 IU; serum protein 6.9 gm/dl; albumin/globulin – 3.6/4.2 gm/dl. PT INR was 2.6. Serum LDH – 1,050.

HbsAg, anti-HCV, anti-HAV were negative. IgM anti-HEV was positive.

Anti-nuclear, anti smooth muscle, and anti-LKM antibodies were negative. Serum ceruloplasmin was 0.65 gm/L (normals 0.25 to 0.63 gm/L). 24-hour urinary copper – 125 microgram/24hr (N< 60 microgram/2hr).

Direct and indirect Coombs' test and osmotic fragility test was negative. On slit lamp examination Kayser-Fleischer (K-F) rings were present. USG abdomen showed liver 16.3 cm in size, normal echogenicity. CECT abdomen showed hepatomegaly with partially contracted gall bladder with oedematous wall with possibility of hepatitis and splenomegaly. MRI brain showed T1 hyperintensity in bilateral gangliocapsular and cerebral peduncle region compatible with Wilson's disease. Liver biopsy was not done due to coagulopathy.

The routine treatment for acute liver failure was started and the patient showed improvement during stay in hospital and came out of hepatic encephalopathy. Zinc acetate – 50 mg three times a day – was started for Wilson's disease. At the time of discharge, serum bilirubin was 28 mg/dl.

Discussion

In patients presenting as fulminant hepatic failure, fulminant presentation of Wilson's disease should also be considered.

Fulminant Wilson's disease is characterised by severe derangement of LFT, encephalopathy, and haemolysis.

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The diagnosis in fulminant Wilson's disease can be difficult because serum ceruloplasmin may be falsely raised as it is an acute phase reactant, as was in our case, or it may be low, owing to liver cell failure. Liver biopsy may be difficult due to coagulopathy. Diagnosis is assisted by increased urinary copper and Coombs' negative haemolytic anemia. ALT and AST are only mildly raised[2]. Our patient had evidence of increased urinary copper excretion and Coombs' negative haemolytic anaemia.

Hepatitis E is the most common cause of acute viral hepatitis in south-east Asia. In India, hepatitis E accounts for 20 – 50 % of acute viral hepatitis[3]. HEV infection never develops into chronic or long-term illness. Hepatitis E is more severe than Hepatitis A with death rates of 1 - 2%.

Some studies have shown infection with HEV to cause severe illness in patients with chronic hepatitis and chronic alcoholic liver disease, but there are few studies on the effect of hepatitis E on other types of CLD.

Monga *et al*[4] and Kumar *et al*[5] showed that HEV infection frequently causes severe decompensation in liver cirrhosis.

There are only two case reports showing viral hepatitis as a cause of decompensation in Wilson's disease. Sallie *et al*[6] reported fulminant liver failure caused by Hepatitis E super infection on an undiagnosed case of Wilson's disease. Ozcay *et al*[7] reported a case of liver failure in Wilson's disease with hepatitis E super-infection, in which the patient succumbed to the illness. Our patient presented with acute liver failure with no previous history of liver disease. After the total work-up, our conclusion was that the disease was hepatitis E super-infection on Wilson's disease.

The deterioration of liver function in this patient leading to hepatic failure was caused by super-imposed acute hepatitis. Fulminant hepatitis from HEV infection is common in pregnant females but rare otherwise. The acute viral insult on underlying Wilson's disease may have caused release of free copper provoking haemolysis and more severe liver damage. Also, pre-existing Wilson's disease may have led to the exacerbation of consequences of hepatitis E.

In conclusion, this case suggests that viral infection may play a part in the acute decompensation seen in some cases of Wilson's disease with increased morbidity and mortality.

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– Editor

"The tragedy of life is not that it ends so soon, but that we wait so long to begin it."

– W. M. Lewis.

CASE REPORT

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Pharyngeal and laryngeal palsy: Unusual manifestation of acute rhuematic fever

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Abstract

Acute rheumatic fever is a multisystem disease. The manifestations of acute rheumatic fever are due to an autoimmune reaction, which leads to damage to human tissues as a result of cross-reactivity between epitopes on the organism and the host. Patients with acute rheumatic fever sometimes present with atypical signs and symptoms. In these circumstances, the Jones criteria may not be sufficient to make a clinical diagnosis. The pharyngeal and laryngeal palsy may be part of this reaction, which is very unusual and to the best of our knowledge has never been reported in the past; hence, we report this case of acute rheumatic fever with pharyngeal and laryngeal palsy.

Key words: Jones criteria, pharyngeal palsy, rheumatic fever.

Introduction

Acute rheumatic fever is non-infective sequelae of pharyngitis caused by group A beta-haemolytic streptococcus[1]. Symptoms usually appear two to three weeks after the initial infection. The incidence of ARF has declined dramatically due to the introduction of antibiotics as well as a change in the M protein of the streptococci leading to alterations in rheumatogenicity. While the exact mechanism of ARF is incompletely understood, autoimmunity is thought to play an important role in the initiation of tissue injury resulting into multisystem involvement[2].

Case report

A 15-year-old female presented with complaint of fever which was moderate-to-high grade for 3 months, tender swollen knee joints since 7 days, swelling over the face and lips, nasal regurgitation of food, and difficulty in speech for 3 days, cough without expectoration for 3 days. Also, there was a positive history of sore throat, followed by symmetrical, migratory, polyarthritis since 7 days. Clinical examination revealed a conscious, well-oriented patient with high-grade fever (102° F), and tachycardia. Facial and perilabial oedema was present. Locomotor system examination revealed difficulty in walking due to swollen, tender joints and restricted passive and active movements. Neurological examination revealed difficulty in speech, palatal and bulbar palsy. Rest of the CNS examination was within normal limits.

Investigations showed a positive CRP and high ESR. Her TLC was 21,100 (N75, L24, E1) with high ASO titre (> 200 Todd units). Throat swab culture was positive for Streptococci. 2D echo examination showed a normal mitral valve and aortic valve without any evidence of AR and MR. LV function was within normal limits. Upper GI endoscopy was normal. X-ray of knee joint showed no abnormality. ANA was negative; HIV 1 & 2 was negative; TFT was WNL. MRI (brain) revealed a calcified granuloma in the convexity of the parietal lobe. Indirect laryngoscopy showed palatal palsy and bilateral vocal cord abductor palsy.

The patient was kept on nasogastric tube for feeding, injectable steroids, oral erythromycin via NG tube. The patient responded and oedema disappeared in 7 days of starting the treatment, but with no improvement in regurgitation and speech. Steroids were tapered to stop; injection benzathine penicillin was started after skin sensitivity testing and given after every 3 weeks. Patient was discharged with NG tube in place, and reviewed after 2 weeks. Signs of clinical improvement were noticed the in form of oral tolerance for sips of water, and indirect laryngoscopy revealed around 50% improvement in vocal cord abductor palsy. 2 weeks later, the patient came with complete clinical improvement with 100% improvement in pharyngeal and laryngeal palsy. NG tube was removed and the patient was kept on penicillin prophylaxis.

There is a high probability of rheumatic arthritis in this case as the patient has a symmetrical migratory polyarthritis with large joint involvement associated with minor criteria like fever, increased ESR, CRP, and leucocytosis, supported by evidence of previous streptococcal infection in the form of positive throat culture[3,4,5]. In our case there was no evidence of rheumatic carditis, as aortic and mitral valve morphology was found to be normal and without any evidence of regurgitation.

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These are usual manifestations of acute rheumatic fever, which are commonly seen and reported, but this patient had pharyngeal and laryngeal palsy which are unusual manifestations and to the best of our knowledge, have not been reported till date. Hence, we report this case as an unusual manifestation of acute rheumatic fever.

Discussion

Acute rheumatic fever (ARF) is a major problem in the developing countries and south-east Asia, with a high prevalence and possible unusual manifestations. Acute rheumatic fever is an immunologically mediated sequel of group A streptococcal infection, which can affect a number of different tissues such as the heart, joints, and brain. ARF can mimic many other diseases of various organs. Because no clinical and laboratory finding is pathognomonic for ARF, the diagnosis can be established by the Jones criteria and an absolute requirement for evidence of antecedent group A streptococcal infection. Positive throat cultures are obtained only in about 11% at the time of presentation[8]. In the paediatric age group, patients of acute rheumatic fever may present with cough, abdominal pain, and epitaxsis[6]. Abdominal pain in epistaxsis occurs only in about 5% of patients. Abdominal pain is usually epigastric or periumblical in location, but may be associated with guarding of abdomen. This pain may be confused with pain of acute appendicitis. These atypical manifestations usually appear days before the major illness. Pathophysiology of acute rheumatic fever is still incompletely understood with different animal models. The present understanding of its pathogenesis indicates that it is an immunologically medicated phenomena and the initial infection in a genetically predisposed person leads to activation of T cell and B cell lymphocytes by streptococcal antigen and super-antigen[7] which results in production of cytokines and antibodies directed against streptococcal carbohydrate and myosin. Laryngeal and pharyngeal palsies are sometimes the presenting features of certain acute and chronic diverse autoimmune diseases like Gullian Barré syndrome and chronic axonal neuropathy, probably the similar mechanism of autoimmunity has led to development of these unusual complications in our patient. In our case, one of the possible explanation of the associated pharyngeal and laryngeal palsy is associated auto-immune vasculitis which can present as lower cranial nerve palsy. The diagnosis of ARF is based on certain clinical criteria.

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"He who is of a calm and happy nature will hardly feel the pressure of old age, but to him who is of an opposite disposition, youth and age are equally a burden."

– Plato.

CASE REPORT

JIACM 2013; 14(3-4): 257-9

Diffuse skeletal involvement and pathological fractures in a case of hyperparathyroidism

BL Bhardwaj, Gurkirat Kaur Gill*****, Ashish Bhagat**, Gurpal Sachdeva***, Rajesh Goyal****, Harnoor Singh Bhardwaj*******

Abstract

Primary hyperparathyroidism is usually diagnosed as an incidental finding of hypercalcaemia in blood tests or due to symptoms secondary to the high calcium. Overt bone disease is an extremely rare presentation. Fractures in hyperparathyroidism are unusual and usually affect the vertebrae. The leading sign of disease is hypercalcaemia due to higher resorption of calcium from bones, decreased urinary elimination of calcium, and higher absorption of calcium in the bowels.

This paper presents the case report of a 19-year-old female patient admitted in our hospital in June, 2011. She came to our hospital in poor general condition with inability to walk and bowing of both legs along with severe pain.

After clinical and radiological examination it was concluded that she was a case of hyperparathyroidism.

Introduction

Patients who have untreated primary hyperparathyroidism with 'ostitis fibrosa cystica' have become a rarity. Primary hyperparathyroidism is usually diagnosed as a result of a chance finding of raised serum calcium or complications associated with hypercalcaemia such as polyuria, polydipsia, muscle weakness, gastrointestinal upsets, and renal stone formation. Bone disease is rarely overt. Radiographic manifestations are seen in less than 2% of patients and include subperiosteal erosions, diffuse osteoporosis, cystic lesions (brown tumours), pathological fractures, 'salt and pepper' mottling of skull, and loss of lamina dura in the mandible[1].

The reported incidence of fractures in hyperparathyroidism is quite low, about 10% in two large series and apart from vertebral compression fractures, no characteristic fracture pattern have been described.

Extensive bony involvement with pathological fractures as a presenting feature due to parathyroid carcinoma has been documented[2], but multiple pathological fractures, as a presenting feature of primary hyperparathyroidism due to parathyroid adenoma is extremely rare.

Case report

A female patient, 19-year-old, hospitalised in our centre in June, 2011 with the complaints of an inability to walk, bowing of legs, and pain in both legs since the last six months. Symptoms were gradually progressive until recently when the patient became confined to bed for the last few weeks. She also reported gastric symptoms like poor appetite and weight loss. Her menstrual cycles were regular. Three years earlier, she had a mandibular operation in an institution when a resection of jaw was performed because of cystic changes. Now she felt severe pain in both the legs.

Having completed the clinical examination, we found that the patient was afebrile, pale. Neck examination was normal. General physical examination and systemic examination was also normal. Extremities were painful on palpation and movement.

Based on clinical findings and laboratory data, a diagnosis of primary hyperparathyroidism was made.

Laboratory analyses revealed:-

Hb 7gms (normocytic normochromic), blood counts were normal, blood urea 22mg/dL, serum creatinine 1 mg/dL, serum corrected calcium was 9.4 mg/dL, serum phosphorus 3.9 mg/dL, serum alkaline phosphatase was raised 2,253 IU/L, serum PTH 1,900 pg/ml (normal value upto 53 pg/ml).

USG Neck: Showed a well-defined heterogeneous hyperechoeic mass seen in the suprasternal region below the left lobe of the thyroid (size 1.7 x 2 cm).

CT Scan: Showed a neck mass with multiple bony lytic lesions with bilateral renal calculi and left ureteric calculi with left hydro-ureteronephrosis with pancreatic calcification.

FNAC knee joint: Showed a few benign-looking giant cells of osteoclast type.

X-ray pictures of the patient showing osteolytic lesions in

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the whole skeleton, and pathological fractures are shown here (Fig. 1, 2, 3).

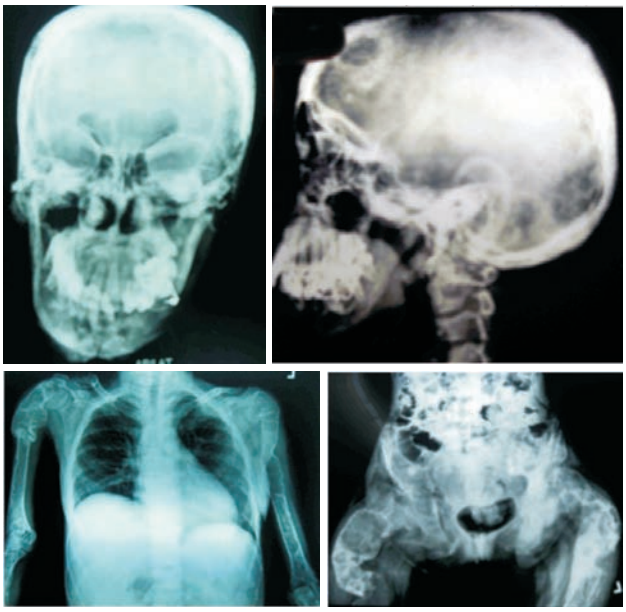

Fig. 1: *X-rays showing diffuse osteolytic lesions in skull, pelvis, lower limb, and upper limb – but sparing the spine.*

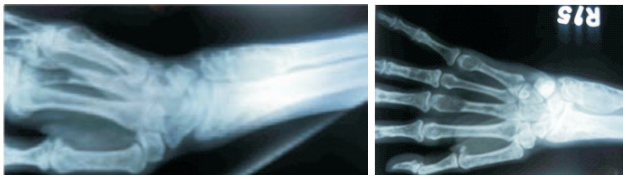

Fig. 2: *X-rays of hand showing diffuse osteolytic lesions.*

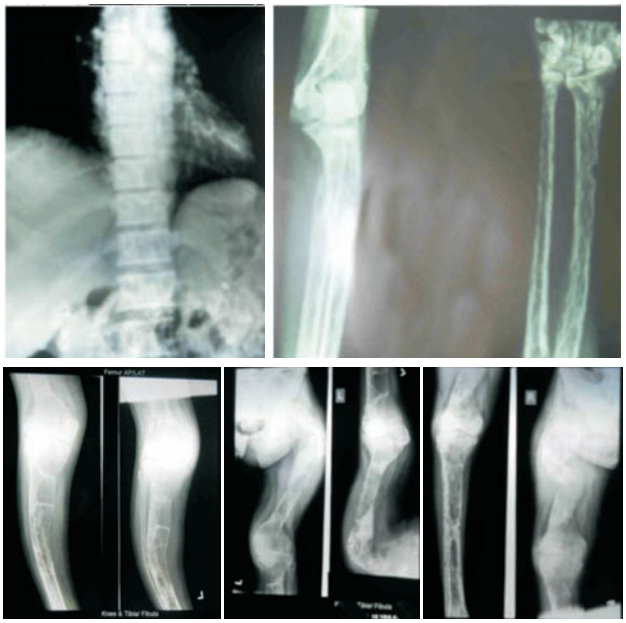

Fig. 3: *X-ray showing osteolytic lesions in lower limb bones along with marked deformities and pathological fracture.*

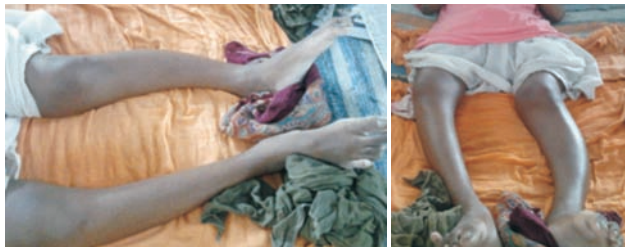

Fig. 1: *Picture showing marked deformity of lower limbs of the patient.*

After considering the clinical, biochemical, and radiological findings, a diagnosis of hyperparathyroid adenoma with advanced bone disease was established. The patient was referred to a higher centre for specialist surgical management.

Discussion

The incidence of primary hyperparathyroidism (PHPT) is suggested to be 1 in 1,000 of the population[3]. The commonest pathology, a solitary adenoma, forms about 80% of the cases. The remaining causes are equally divided between multigland adenomata and diffuse hyperplasia. Carcinoma is the rarest cause and forms less than 2% of cases[4]. The differentiation between carcinoma and adenoma is difficult and local invasion beyond the capsule, presence of distant metastases, and local recurrence after excision are often the principal diagnostic criteria for a carcinoma[5].

Primary hyperparathyroidism is considered rare in developing countries, but recent experience has shown that its apparent rarity may be due to paucity of reports from these countries and also to limited diagnostic facilities. The advent of automated serum biochemical analysis has highly augmented its diagnosis and has made asymptomatic hypercalcaemia its commonest presentation in the developed countries, whereas in many developing countries, patients usually present with metabolic bone disease and multiple fractures[6].

The incidence of metabolic bone disease in patients with PHPT in developing countries is very high[7,8]. The reasons advanced for this is the high prevalence of protein, vitamin D and dietary calcium deficiencies and the high dietary phytate and phosphates in some cultures. The protein deficiency can further reduce total serum calcium since 50% is bound to albumin. These patients therefore, tend to be normocalcaemic even after the correction of hypoabluminaemia. Our patient is a typical example and similar findings have been noted in previous reports. It is therefore pertinent for clinicians practicing in the developing countries to note that nutritional deficiencies can be seen in their patients, unlike those from the

developed nations, making hypercalcaemia irrelevant in the diagnosis of PHPT. Hence, serum calcium level may not be part of the criteria for surgical intervention, contrary to what was earlier suggested. The diagnosis of normocalcaemic primary hyperparathyroidism (PHPT) can be made in subjects whose total and ionized serum calcium are completely normal, but in whom the PTH level is persistently elevated. In order to make the diagnosis of normocalcaemic PHPT, secondary causes for an elevated PTH level should be ruled out, such as vitamin D insufficiency, or renal insufficiency. Replacing the former patients with vitamin D to reach levels now considered to be normal (i.e., > 30 ng/ml) often returns the PTH to normal. Occasionally, however, these patients will become hypercalcaemic with vitamin D replacement, thus unmasking more typical hypercalcaemic PHPT. If the PTH remains elevated and the serum calcium remains normal following vitamin D repletion, and other causes of an elevated PTH have been excluded, then the diagnosis of normocalcaemic PHPT can be considered[9]. Parathyroidectomy is the treatment of choice in PHPT. Success of the surgery is determined largely by early diagnosis and localisation of the adenoma before surgery[10,11]. Despite the late presentation of our case, the diagnosis was assisted by radiographic studies including CT and the assay of the parathyroid hormone. These pre-operative investigations made decisions for early surgery possible. Sudden post-operative hypocalcaemia may be a major complication. The incidence of this hungry bone syndrome is likely to be high in our environment due to the associated pre-operative dietary calcium and vitamin D deficiency. Therefore, this potential complication should be anticipated and aggressive nutritional support to address these deficiencies must be instituted appropriately.

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CASE REPORT

JIACM 2013; 14(3-4): 260-2

Peripartum cardiomyopathy – Unusual observations

Sunita Gupta, Parveen Gupta*, Amandeep K Dhaliwal***

Abstract

Lower extremity arterial thromboembolism is a rare initial presentation in patients of peripartum cardiomyopathy. Besides, peripartum cardiomyopathy can itself be the initial manifestation of familial dilated cardiomyopathy. We present a case having these atypical observations.

Key words: Familial dilated cardiomyopathy (FDC), lower extremity arterial thromboembolism.

Introduction

Peripartum cardiomyopathy (PPCM) is the development of heart failure in the last month of pregnancy or within the first 6 months postpartum, but there is no evidence of any other demonstrable cause for cardiac failure or any structural heart disease before the last month of pregnancy[1]. Although viral, autoimmune, and idiopathic factors may be contributory, its aetiology remains unknown. Peripartum cardiomyopathy usually presents initially with signs and symptoms of heart failure and rarely with thrombo-embolic complications[2]. The criteria for familial dilated cardiomyopathy (FDC) are fulfilled when one individual is diagnosed with idiopathic dilated cardiomyopathy (DCM) in a family, with at least: one relative also diagnosed with idiopathic DCM-or-one first-degree relative with an unexplained sudden death under the age of 35 years[3].

We report an unusual case of PPCM in a previously healthy woman who presented with an acute ischaemia of one leg, highlighting that this finding can be the initial manifestation of peripartum cardiomyopathy besides having a familial occurrence.

Case report

A 22-year-old female presented to the emergency with sudden onset of pain and numbness in left leg of 1 day duration. There was no history of any trauma, no symptoms/signs suggestive of inflammation, no history of alcohol or drug abuse, and no previous history of cardiovascular disease. She had no significant medical or surgical history. Her obstetric history revealed that she had delivered a male baby 2 months ago; the delivery was full term, uneventful, normal vaginal delivery with no prolonged immobilisation. Family history was significant in the context of her elder sister having expired one year ago at the age of 25 years soon after delivery of her second child; and in the language of relatives, she was told by the doctors that she died of a "large" heart.

At admission she was afebrile, her blood pressure was 108/70 mm Hg, pulse rate 90/min, and had oxygen saturation (SpO_2) of 98%. Her respiratory exam revealed scant basal crepts. The cardiovascular exam did not reveal any abnormality. On local exam of her left leg, it was found that it was cool, pale, with non-palpable left dorsalis pedis, post tibial, popliteal, and femoral arteries. The right lower limb was normal on examination. During her second hospital day, the patient developed dyspnoea on exertion, later progressing to orthopnoea, along with productive cough. Her saturation dropped and she had profound hypoxaemia, tachycardia, and hypotension.

Investigations showed Hb –10 gm%, TLC–13, 000/cumm, normal urinalysis, LFTs – raised conjugated bilirubin, and slight elevation of liver enzymes. Her chest X-ray showed cardiomegaly with right-sided pleural effusion (Figure 1). The lower limb Doppler studies showed no venous thrombosis. In fact, no flow was seen in left common femoral artery, left superficial femoral artery, and any arteries further down – suggestive of thrombosis involving left common femoral artery and left superficial femoral artery (Figure 2). Evaluation for hypercoagulative state (APLA and homocysteine) was normal. Also, D-dimer study was negative, which ruled out pulmonary embolism (it was unlikely in view of no venous thrombosis). Transthoracic echocardiography revealed global hypokinesia, severe left ventricular systolic dysfunction, severe mitral regurgitation, and ejection fraction ~19% (Figure 3).

She was anticoagulated with heparin. No attempt was made to address the embolisation of her legs with stenting because of her acute cardiac decompensation and financial constraints. As her cardio-respiratory status deteriorated, she was started on non-invasive ventilation

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and ionotropic support in the form of dobutamine.The patient became haemodynamically stable after 48 hours and she was maintained on diuretics, beta-blockers, and ACE inhibitors. Her legs were asymptomatic and viable but pulses not palpable. She was started on oral anti-coagulants and antiplatelet drugs after the baseline PTI/INR.

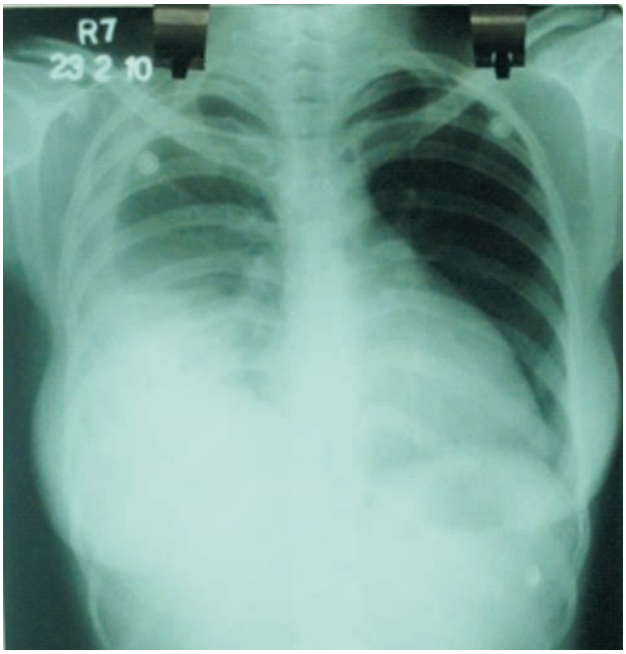

Fig. 1: *Chest X-ray showing cardiomegaly and pleural effusion.*

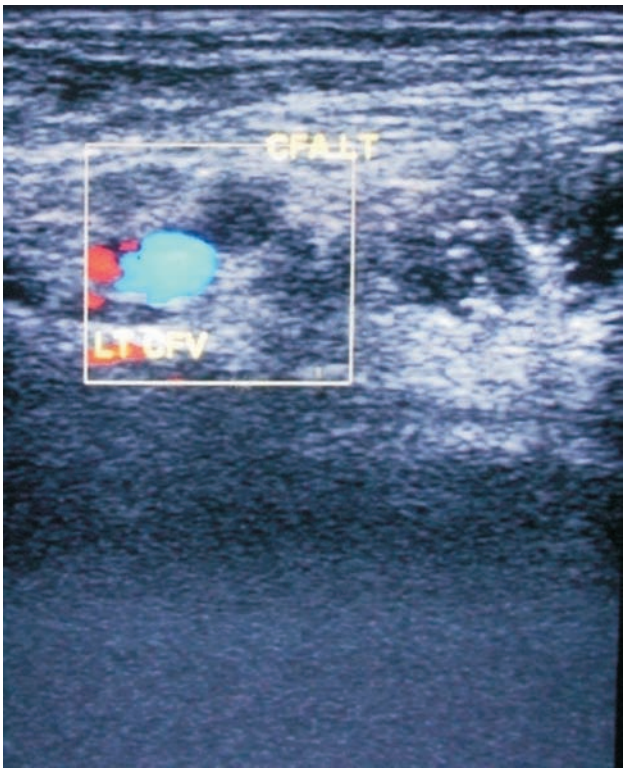

Fig. 2: *Arterial Doppler of left lower limb showing arterial thrombosis.*

Investigations of her first degree relatives – her parents and younger sister – were essentially normal. However, investigations of her brother revealed cardiomegaly and systolic dysfunction with EF 42%.

Based on her findings, her postpartum state and positive family history, a diagnosis of "peripartum cardio-myopathy with familial occurrence with congestive heart failure with left lower limb arterial thrombosis" was made.

The patient was discharged and has been coming for regular check-ups and is symptomatically better, with her left leg asymptomatic and viable and resolution of her heart failure features. Echocardiography shows persistent low EF of ~ 20% and Doppler left lower limb showing collaterals formation with no flow in the main arterial vessels. She continues to be on digoxin, antiplatelets, oral anti-coagulants, and ACE inhibitors.

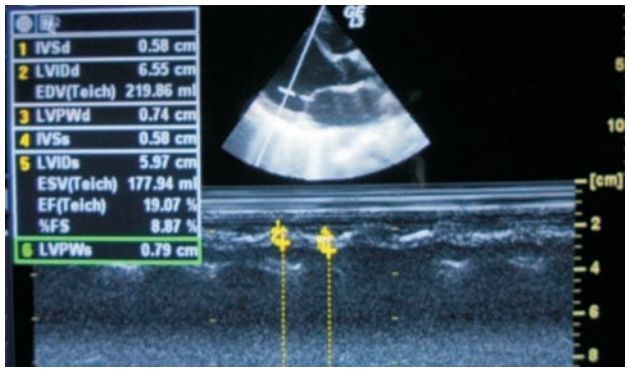

Fig. 3: *2-D echocardiogram showing dilated cardiomyopathy.*

Discussion

Venous thromboembolism is an important cause of maternal morbidity and mortality. The risk of venous thromboembolism is greater in older women, in women who have an operative delivery, obesity, high parity, and immobilisation, and with acquired or inherited thrombophilias. But arterial thrombosis is uncommon in pregnancy; may have devastating consequences[4]. Peripartum cardiomyopathy is a rare life-threatening cardiac condition that can foster intracardiac thrombosis and produce peripheral vascular complications through embolisation. Probable sites of embolisation which are seen can be cerebral, pulmonary, or renal[5]. In patients with PPCM, the return of the left ventricle size and function to normal in the first 5 months of the postpartum period is a good prognostic factor. This usually occurs in 50% of patients with PPCM. Our patient's left ventricular dysfunction persisted greater

than 6 months after hospital discharge.

The present case demonstrates non-cardinal symptoms especially "ischaemia threatening a limb" as an extraordinarily rare initial presentation of PPCM. The early recognition of arterial thromboembolism as a result of PPCM may prevent further morbidity and mortality of this disease; hence underscoring the importance of rapidly recognising this disorder[6]. This case also demonstrates that PPCM can be the first manifestation of familial DCM. This case is considered as familial because of history of SCD in the sister, and the brother shows evidence of cardiomyopathy. It is recommended that presymptomatic screening be carried out for covert DCM in first-degree family members of PPCM patients without recovery of left ventricular function and dimensions.

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BOOKS RECEIVED

Diabetes Mellitus

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Now in its 4th edition, "Diabetes Mellitus" is fully revised and updated. It includes topics like newer therapeutic agents -- DPP-4 inhibitors, extenatide, liruglutanide, and glitazones. Conventional versus tight control of diabetes with their merits and demerits are discussed. Current guidelines on control of diabetic patients are outlined. Relationship of anti-diabetic drugs to cancer and cardiovascular risk are highlighted. Childhood obesity, type-2 diabetes in children, stem cell therapy, pancreatic transpantation, and metabolic syndrome are discussed. There are 93 chapters in this edition (including 10 new chapters). Overall, this is an exhaustive and well-written book which takes into consideration the Indian context. This book is ideally suited to the needs of medical students, teachers, internists, and practising physicians as a desktop reference book. With 807 pages and the modest price of Indian Rs.450/-, this book is a pleasure to read because of its simple language and style. Its author Dr. P.G. Raman is former Professor & Head, Department of Medicine, M.G.M. Medical College and M.Y. Hospital, Indore, Madhya Pradesh.

CASE REPORT

JIACM 2013; 14(3-4): 263-5

Adult onset Still's disease – A test of the clinician's perseverance

Kavita Krishna, Gagan N Jain**, Karan Topiwala****

Abstract

Adult onset Still's disease (AOSD) is a rare variant form of systemic onset juvenile rheumatoid arthritis. AOSD can present with prolonged fever and joint pains with all the investigations for infection and autoimmune disease being negative. If the acute phase reactants are raised then we should suspect AOSD as a diagnosis by exclusion. We present two cases of AOSD; both presented with long standing fever and anemia. After thorough investigation, having ruled out various infections and auto immune conditions, we arrived at the diagnosis of AOSD by exclusion. Both the patients responded to treatment.

Introduction

Adult onset Still's disease (AOSD) is a rare variant of systemic onset juvenile rheumatoid arthritis (JRA). JRA was formerly known as Still's disease. Currently no consensus is present on whether AOSD and paediatric Still's represent the same disease in continuity, rather than being distinct entities. Despite sharing similarities in pathogenesis especially the cytokines (IL-6, IL-18, TNF-alpha) they vary in the levels of acute phase reactants and prognosis[1]. AOSD is a diagnosis of exclusion as it lacks a pathognomonic feature or a specific sero-pathological marker. It has a varied clinical presentation, often masquerading as malignancies (leukaemia, lymphoma), infections (viral – rubella, hepatitis B, coxsackie, parvovirus B19 or bacterial – tuberculosis, Brucellosis, Lymes disease), connective tissue disorders (systemic lupus erythematosus (SLE), mixed connective tissue disorders (MCTD), vasculitis (Takayasu's arteritis), and granulomatous disorders (sarcoidosis, Crohn's disease)[2].

Case report

Case 1

A 25-year-old female presented with fever, dull aching pain and swelling in her right knee since 20 days, followed by pain in the left knee after 2 days. Pain increased on walking and subsided at rest. There was history of similar episode previously, for which she had been admitted. Pain was accompanied by reduced appetite and generalised weakness. There was mild pallor and splenomegaly. There was no rash or muscle tenderness.

Investigations revealed an elevated ESR (95 mm/first hour), CRP (22 mg/dl), TLC (28,700/cu mm) and haemoglobin 10 g%. On admission the patient showed ESR – 57mm at the end of first hour; CRP – 28 mg/dl; TLC – 16,800/cu mm; platelet count – 440,000/cu mm; Hb – 8.5g%. 24-hour urine albumin (500 ml) - 185. All biochemical investigations were within normal limits. HIV, HbsAg, peripheral smear for malarial parasite and Mantoux test were negative. Coagulation profile was normal. Ultrasound abdomen revealed hepatosplenomegaly, and chest x-ray was normal. Bone marrow examination showed a reactive marrow aspirate with features of a chronic disorder. RA factor and ANA was negative. So SLE and MTDC were unlikely.

The diagnosis of AOSD was suspected and blood sent for serum ferritin level which was found to be elevated; values on 1:10 dilution – more than 800 ng/ml (N: 81 - 400) and on 1:100 was 8,068 ng/ml. This supported our clinical diagnosis.

Case 2

A 25-year-old healthy male, developed high-grade intermittent fever with chills and rigors, joint pains associated with swelling of the wrist, MCP, PIP joints, and generalised weakness since two months. He was admitted elsewhere and treated with ciprofloxacin, prednisolone and cetirizine for three days without relief of symptoms; also given was a course of chloroquine, lumefantrine, and artemether.

Patient was afebrile and had tachycardia (pulse: 110/min) and blood pressure of 130/80 mm Hg. He had mild pallor and splenomegaly. Wrist, MCP, and PIP joints were swollen and tender with restriction of movement in all directions. Rest of the systemic examination was normal.

Investigations revealed a fall in the Hb and TLC values from 14.4 g% and 14,400/cu mm to10.8 g% and 8,400/cu mm respectively over a period of one month. Patient was negative for MP, Leptospira antigen, and Widal. On his admission, TLC and Hb values were 9,400/cu mm and 9.5 g%, differential count was N-81, L-15, E-02, M-02, B-

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00; platelets were 3,63,000/cu mm; the peripheral blood smear [PBS] was normocytic normochromic with a few atypical lymphocytes; ESR – 62 mm/hour CRP – 33.64 mg/dl. Serum protein/albumin: 7.8/3.1 mg% and his LFTs: SGOT/SGPT/ALP at 58/99/55 IU/L and STB [serum total bilirubin] and direct at 1.07/0.59 mg/dl. Renal function and coagulation profile was normal. Rapid malaria test, Dengue, HIV, HBsAg, RA factor and ASO was negative. Over the course of admission SGPT/SGOT values increased to 60/97 IU/L. Bone marrow was reactive with a mild erythroid depression; blood cultures and PCR-TB was negative, while Brucella (Ig G and IgM) was negative and borderline positive respectively. Chest x-ray was normal, and ECG showed sinus tachycardia. Mild AML prolapse and trivial MR was visible on 2D Echo, the LVEF was 70%; no vegetations were seen. Ultrasound of abdomen showed borderline splenomegaly. Considering the affection of small joints of the hand, intermittent fever, and laboratory investigations, serum ferritin values were sent and found to be at 20,105 ng/ml (N: 81-400). Patient was diagnosed as an acute case of AOSD.

Discussion

AOSD occurs world over with an estimated 1.5 cases per 0.1 - 1million population with a bimodal age distribution with 2 peaks at 15 - 25 and 36 - 46 years, females slightly more than males. It is however also known to occur in older people, some more than 60. Aetiology of AOSD is unknown, although possible aetiologies include infections like viral (rubella, EBV, CMV, HHV 6, hep B And C, Parvovirus B 19, HIV) bacterial (mycoplasma pneumonia, *Chlamydia trachomatis* pneumonia) and parasitic (*toxoplasma gondii*). There is a genetic predisposition; the Japanese are reported to be at a higher risk. Pregnancy, post-partum, stress (physical/emotional) has a strong correlation[3].

The clinical features of AOSD are fever, arthralgia/arthritis, Still's rash, lymphadenopathy and hepato-splenomegaly. Typically, an acute exacerbation is heralded by aseptic, non-exudative pharyngitis concomitant with fever (with negative cultures and no response to antibiotics). MRI may show cricothyroid perichondritis, often along with an increasing fatigue and myalgia. Chronic cases develop anaemia of chronic disorders, alopecia, and significant weight loss. Rare manifestations are sicca syndrome, retinal exudates, transient cranial nerve palsies, peripheral neuropathy, and septic meningitis[4].

In laboratory findings, leukocytosis > 10,000/cu mm (92% cases), > 15,000/cu mm (81% cases) and with > 80% PMNs (88% cases). Often associated with reactive thrombocytosis, with platelet count > 400,000/cu mm (62% cases). Only in < 2% cases, WBC count may below. Raised serum ferritin (70% cases), usual threshold > 1,000ng/ml. Ferritin is an APR (acute phase reactant); the levels are elevated because of increased synthesis by RES in response to cytokines especially Interleukins 18, 1 beta, 6 and TNF alpha. Reduced glycosylated fraction of total serum ferritin, its values drop to less than 20%. LFTs are deranged in 73% cases, however such an increase is often associated with the use of non-steroidal anti-inflammatory drugs. RA factor/ANA negativity is seen in 93% and 92% cases respectively; raised ESR (99% cases), raised CRP, reduced haemoglobin </= 10g/dl (68% cases) and reduced serum albumin (< 3.5 g/dl) 81% cases[5].

Prognosis in AOSD can be divided into: self-limiting (monocyclic), i.e., a single episode lasting less than 1 year followed by persistent good health; intermittent (polycyclic), i.e., a complete remission followed by more than 1 relapse, and chronic disease (approximately 30% - 50%), i.e., a persistently active disease mostly due to established destructive arthritis, though about 25% will enter temporary remission in about a year's time[3].

Treatment of AOSD includes the use of NSAIDs, corticosteroids, immunosuppressants, DMARDs and the newer anti-interleukin drugs. NSAIDs are effective in up to 60% of AOSD patients with indomethacin (2 mg/kg/day) as the most utilised NSAID, although all others may be equally effective when used at comparable anti-inflammatory doses. Corticosteroids are needed in most patients. Prednisolone should also be used in patients who are suffering from persistent anaemia, pericarditis, serositis and marked elevation of liver enzymes. When prednisolone fails, dexamethasone or MPPT (methyl prednisolone pulse therapy) may be successful. Intra-articular steroid can be used in chronic articular disease[6]. Steroid toxicity is a major problem and hence methotrexate (MTX) – an anti-metabolite – may be used particularly for cases with severe arthritis. Besides MTX, other DMARDs such as azathioprine, cyclosporine/tacrolimus (calcineurin inhibitors), leflunomide, and cyclophosphamide have been used for maintenance therapy. Recently, more specific therapy using biologic agents has been developed considering the cytokine mediated pathogenesis of AOSD, especially in cases that do not respond to conventional medications such as corticosteroids and DMARDs. Notable examples include infliximab[7], the monoclonal chimeric anti-TNF-α antibody, adalimumab, which is an injectable anti-TNF protein, etanercept – a TNF blocker; both infliximab and etanercept have been used with success in steroid resistant cases. Anakinra, an IL 1 receptor antagonist, has shown great promise with rapid remissions, even in refractory cases; so has rituximab (monoclonal antibody,

anti-CD20) and tocilizumab, anti-IL-6 receptor monoclonal antibody. Plasmapheresis and IVIG are other modalities of treatment in refractory AOSD.

To conclude, AOSD can often be a diagnostic dilemma as it present with prolonged fever and joint pains. All the investigations for infection and autoimmune disease are negative. Raised acute phase reactants should suggest the physician to suspect this entity. Early treatment is rewarding.

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CASE REPORT

JIACM 2013; 14(3-4): 266-7

Infective endocarditis due to internal jugular vein haemodialysis catheter

Sunil Kumar, SK Diwan**, AK Wanjari**, Chetan Mahure****

Abstract

Central catheter induced endocarditis is a new, health-care associated infective endocarditis (IE) which should be added in categorisation of infective endocarditis because of its increasing incidence. We report the case of a young boy who developed vegetation and endocarditis due to haemodialysis catheter in the right internal jugular vein.

Key words: Infective endocarditis, haemodialysis, catheter.

Introduction

Infective endocarditis (IE) is a relatively rare disease worldwide (1.8 - 7.0 per 100,000) per year[1]. Common categories of infective endocarditis are native valve IE, prosthetic valve IE, IE in intravenous drug users, nosocomial IE, and new health-care associated IE which should be added because of its increasing incidence. Within this new category, IE in haemodialysis patients appears to be the most important subgroup. Here we report the case of an 18-year-old boy diagnosed as chronic kidney disease (stage five) who developed vegetation and endocarditis due to hemodialysis catheter in the right internal jugular vein.

Case report

An 18-year-old tribal boy who was a known case of chronic kidney disease (stage 5) was admitted in our hospital for haemodialysis. After screening for hepatitis B, C, and HIV, a double lumen haemodialysis catheter was inserted in his right internal jugular vein as a vascular access for emergency haemodialysis. After the stability of his clinical condition, arterio-venous fistula was made; but unfortunately, the fistula failed. He developed high-grade fever (39°C) associated with sweating and anorexia after about 4 weeks of dialysis. There was no associated chest pain, cough, haemoptysis.

On examination, the patient looked acutely ill, febrile, pale, tachypnoeic with blood pressure of 140/90 mm Hg. There were no signs of infection at the catheter insertion site. Heart sounds were normal with no murmurs or additional sounds. The chest and abdomen examination was unremarkable.

The investigations revealed TLC of 10,000, Hb – 6.8 gm%. His blood sugar was normal. Three consecutive blood cultures were negative, and a chest radiograph was normal. The patient was given injectable ampicillin and metronidazole for a period of one week but without response. The patient was reviewed again after the repeat of blood cultures which were again negative. Transthoracic echocardiography was done which showed normal-sized heart chambers, with large vegetation (Fig. 1, red arrow). The antibiotic therapy was changed to a combination of vancomycin and gentamicin.

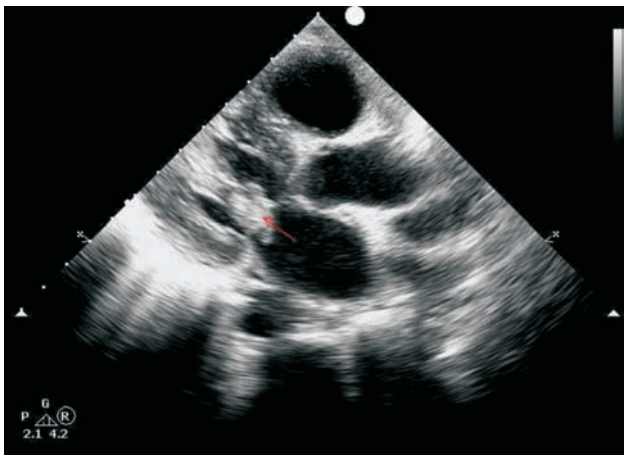

Fig. 1: *Transthoracic echocardiogram showing normal-sized heart chambers, with a large vegetation (red arrow)*

The patient became afebrile on the 3rd day of therapy. Gentamicin was stopped after one week, while vancomycin was continued for a period of 4 weeks. The central venous catheter was removed; catheter tip did not grow any organism. Catheter was inserted in femoral vein for further dialysis. Due to non affordability he was on irregular dialysis and treatment, later on he succumbed to his illness.

Discussion

Infective endocarditis is now affecting many patients, a

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significant proportion of whom have no previously known valve disease, and develop IE as the result of health-care associated procedures. Within this new category, IE in haemodialysis (HD) patients appears to be the most important subgroup[2]. There are several potential explanations for the increased incidence of IE in HD patients. Ageing of dialysis population may act through the increased frequency of degenerative valve lesions. Likewise, valve calcifications, which are extremely frequent in HD patients, may also play a role[3]. However, the most important risk factor seems to result from an increased use of catheters instead of fistulas as vascular access devices[4].

Several hospital-based diagnostic and therapeutic procedures, such as venous catheterisation for haemodialysis, are being performed more frequently, and that has led to the emergence of more cases of nosocomial endocarditis. The most frequent organisms seen in cases of intravenous catheter sepsis are Candida, Pseudomonas, Enterococci and Staphylococci[5]. Polymicrobial infections are also encountered, but less frequently[6]. The negative blood cultures in our patient posed a dilemma in his management. The prior antibiotic intake might have been the cause for the repeatedly negative blood cultures as has been reported in other cases. The risk of infection can be reduced by shaving the area for insertion immediately before introducing the catheters with careful attention to the aseptic techniques during procedures, and adherence to the recommendation of antibiotic prophylaxis.

In conclusion, though such case reports are available[7] our report will serve as an example of keeping a high suspicion index for the diagnosis of infective endocarditis in patients who develop fever while having catheters as accesses for haemodialysis, despite the negative blood cultures. Also because of increasing incidence, such health-care associated IE should be added while categorising the infective endocarditis apart from nosocomial endocarditis.

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CASE REPORT

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A case of pure motor syringomyelia

Bhratri Bhushan Yadav, DC Kumawat***

Abstract

Syringomyelia is a rare disorder with its hallmarks being bi-brachial amyotrophy and dissociated sensory loss. We present here a case of syringomyelia devoid of sensory loss, with only lower motor neuron manifestations (occurring sequentially in both upper limbs) and kyphoscoliosis. It has been described only very exceptionally, for syringomyelia to present without any sensory involvement.

Key words: Amyotrophy, dissociated sensory loss, lower motor neuron, Chiari malformation.

Introduction

Syringomyelia is the presence of a fluid-filled cavity within the spinal cord. In 1546, Eisteinne provided the first pathological description of this rare disorder that classically presents as progressive bilateral brachial amyotrophy and dissociated sensory loss in a cape like distribution. If left untreated, syringomyelia is slowly progressive in more than 50% of patients, and ultimately complete loss of spinal cord function[1] and fatal extension into the medulla is possible. We are reporting a case of syringomyelia with purely motor manifestations without any sensory loss.

Case report

A 50-year-old lady presented with slowly progressive, insidious onset weakness and thinning of right upper limb proximally for 20 years; for about 6 years there was progressive weakness and atrophy of right upper limb distally and she had difficulty doing fine activities of daily living. No activities could be performed since one year. Progressive weakness and atrophy of left upper limb proximally for 5 years and distally for 2 years in the same manner as right upper limb were present. There is history of cervico-thoracic kyphoscoliosis for about 10 years that was progressive in nature. But there was no history of any sensory loss, bladder-bowel symptoms, or bulbar dysfunction, pain, inadvertent trauma, or any chronic infection in the past.

On examination, only motor weakness was present with lower motor neuron (LMN) signs, like gross atrophy of bilateral thenar, hypothenar eminences (right more than left), deltoid, biceps, and supraspinatus (Fig. 1 & 2). Hypotonia was there in both upper limbs, as was the weakness at all joints, fasciculations were present in the upper back. In bilateral lower limbs there were no abnormal findings. Sensory examination was completely normal.

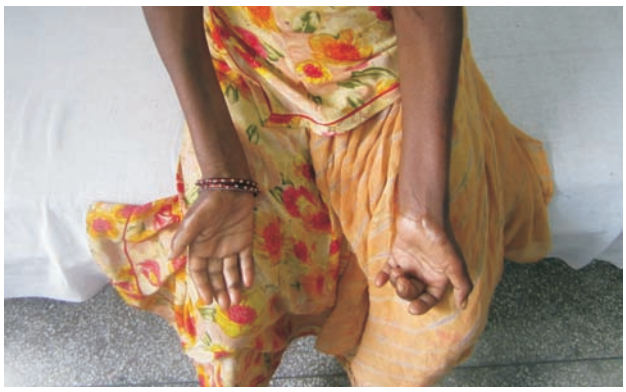

Fig. 1: *Bilateral atrophy of thenar and hypothenar eminences.*

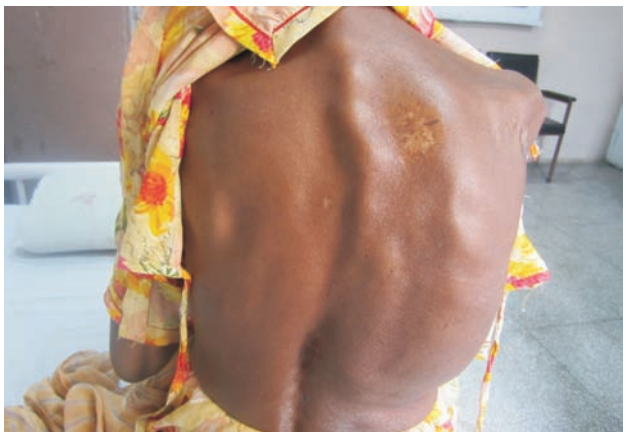

Fig. 2: *Atrophy of supraspinatus, deltoid muscles; and kyphoscoliosis deformity in cervico-dorsal region.*

As the patient had no history of sensory loss, bladder and bowel involvement, and on examination no spastic paraparesis, hence possibility of bi-brachial motor neuron disease was also entertained. On investigation, her blood biochemisty was normal. MRI cervical spine with screening of whole spine revealed a benign syrinx in the cord extending from cranio-vertebral junction to level of 9th -

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10th thoracic vertebrae; no enhancement on contrast was seen, and there was marked kyphoscoliosis deformity in the cervico-dorsal region. ENMG was done and there was chronic denervation in cervico-thoracic myotomes but sensory involvement was not there as SNAP (sensory nerve action potentials) were normal.

The patient was referred for neurosurgical opinion and was advised surgery that she has yet to undergo.

Discussion

Syringomyelia (from the Greek *syrinx*, "pipe" or "tube") is defined as a chronic progressive degenerative or developmental disorder of the spinal cord, characterised clinically by painless weakness and wasting of the hands and arms (brachial amyotrophy) and segmental sensory loss of dissociated type (loss of thermal and painful sensation with sparing of tactile, joint position, and vibratory sense)[2]. The most frequent orthopaedic association of syringomyelia is scoliosis. Syringobulbia refers to the extension of the syrinx into the brainstem; hydromyelia and syringohydromyelia are abnormal enlargements of the central canal of the spinal cord. The major causes of syringomyelia are Chiari malformation, foramen magnum obstruction, communicating hydrocephalus, trauma, spinal cord tumour, infection, inflammation, cervical spondylosis, and idiopathic[3].

Our case was special because there was no sensory loss both examination-wise and upon electrophysiological testing. It is only exceptionally that a patient with syringomyelia will present with only motor involvement without any sensory loss.

The epidemiology is related directly to the primary disease process. No study adequately explains the pathophysiology of syringomyelia. A common feature in many forms of syringomyelia is a derangement or obstruction of the normal circulation of the CSF (cerebrospinal fluid) at or below the foramen magnum. In Chiari malformations, Heiss *et al* have demonstrated the presence of pressure waves in the upper cervical subarachnoid spaces that may lead to progressive syringomyelia[4]. In post-traumatic, post-infectious and post-inflammatory syringomyelia, the derangement occurs below the foramen magnum in the spinal cord[5].

Disease progression, as seen in 50% of cases, can lead to progressive motor, sensory, and sphincter dysfunction. Also progressive sensory involvement may lead to severe intractable dysesthic pain. In rare cases, syringomyelia has been reported to spontaneously resolve[6].

MRI with T1 and T2 weighted images is the diagnostic modality of choice, but CT scan with contrast may be used when MRI is contraindicated. MRI determines the choice of management strategies.

Proper treatment of syringomyelia depends on accurately identifying its cause. Treatment options are mainly surgical with medical management having limited use. First-line treatment options are sub-occipital craniectomy with duraplasty for Chiari associated syrinxes, ventriculo-peritoneal shunt for intracranial hydrocephalus, restoring subarachnoid space with adhesiolysis and duraplasty in post-infectious, post inflammatory, and post-traumatic syringomyelia. The second-line treatment for all types of syringomyelia is placement of a syrinx shunt. Serial neurological examinations and serial MRI studies are important for monitoring of surgical outcomes.

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"Any man who reads too much and uses his own brain too little, falls into the lazy habit of thinking."

– Albert Einstein.

CASE REPORT

JIACM 2013; 14(3-4): 270-2

Wilson's disease – Early detection and treatment improves outome

VK Katyal, Tarana Gupta**, RK Goel***, Kunal Mahajan****, Shalini Agarwal******

Abstract

Wilson's disease is an autosomal recessive familial disorder due to an inborn error of copper metabolism. It is characterised by multiorgan involvement due to excessive deposition of copper in various organs. After the second decade of life, 75% of the cases present with neurological involvement, and we report such a case who presented with various neurological features and had asymptomatic hepatic involvement.

Key words: Wilson's disease (WD), hepatic, neurological, hepatolenticular degeneration.

Introduction

Wilson's disease (WD), also known as hepatolenticular degeneration, is a familial disorder inherited as an autosomal recessive trait, localised to chromosome 13. It is an inborn error of copper metabolism due to reduction in synthesis of ceruloplasmin, a copper transport protein, which results in accumulation of excessive copper in various organs, viz: brain, liver, cornea, and kidneys. Gross pathology of the CNS involves grey and central white matter in bilateral symmetrical manner of putamen, caudate nucleus, thalamus, globus pallidus, dentate nuclei, pons, and mesencephalon. This results in incoordination, tremor, dysarthria, dystonia, rigidity, and difficulty in fine motor tasks. Hepatic involvement on the other hand may have various presentations of acute hepatitis, chronic hepatitis, cirrhosis of liver and acute fulminant hepatic failure. We report here a case who presented with florid neurological involvement in the 2nd decade, and has asymptomatic hepatic involvement.

Case report

A 17-year-old male presented to our medicine OPD with involuntary movements of the right hand which were coarse tremors at rest, and increased with activity since 8 months. There was no history suggestive of ataxia and incoordination. The patient revealed no history of seizure and loss of consciousness. He had a depressive mood with decreased interest in surroundings and suicidal thoughts. He was a student of 10 + 2 with poor school performance since two years.

His general physical examination was normal with stable vitals and no icterus. Central nervous system examination revealed normal mentation with mini mental status score of 28/30. There were wing beating type coarse tremors in the right hand at wrist joint. Tremors were present in the tongue also. His right ankle reflex was exaggerated. Tone was increased in all four limbs involving flexor and extensor compartments – lead pipe type. Cranial nerves, motor, sensory, and cerebellar systems were unremarkable. Per abdomen examination revealed a soft, non-tender liver, palpable 2 cms below the costal margin with liver span 17 cm. No flank dullness in abdomen was detected.

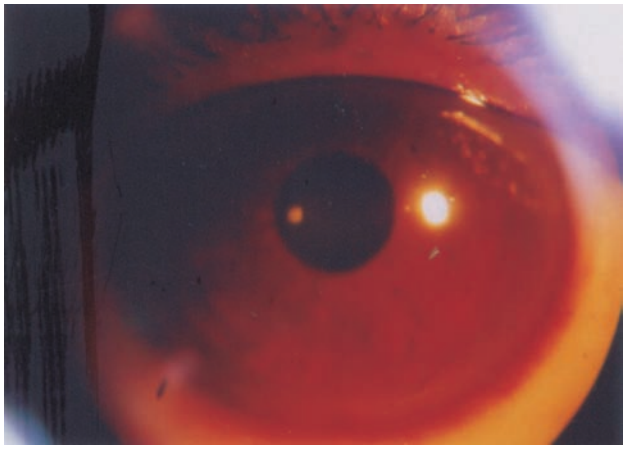

Fig. 1: *Slit lamp examination showing diffuse illumination depicting Kayser-Fleisher ring.*

On investigations, haemogram showed Hb – 12.4 gms%, TLC – 6,000/cumm, DLC: P-60, L-36, M-03, E-01, B-01%, platelet count 100,000/cumm. Serum bilirubin total was 1.05 mg/dl, direct 0.25 mg/dl, indirect 0.80 mg/dl, serum glutamic oxaloacetic transaminase (SGOT) - 48 U/L, serum glutamic pyruvic transaminase (SGPT) - 25 U/L, alkaline phosphatase – 80U/L, gamma glutamyl transpeptidase (GGTP) - 21 U/L. 24-hour urinary copper was estimated and it was significantly elevated to 593 µg/dl (N: 20 - 50

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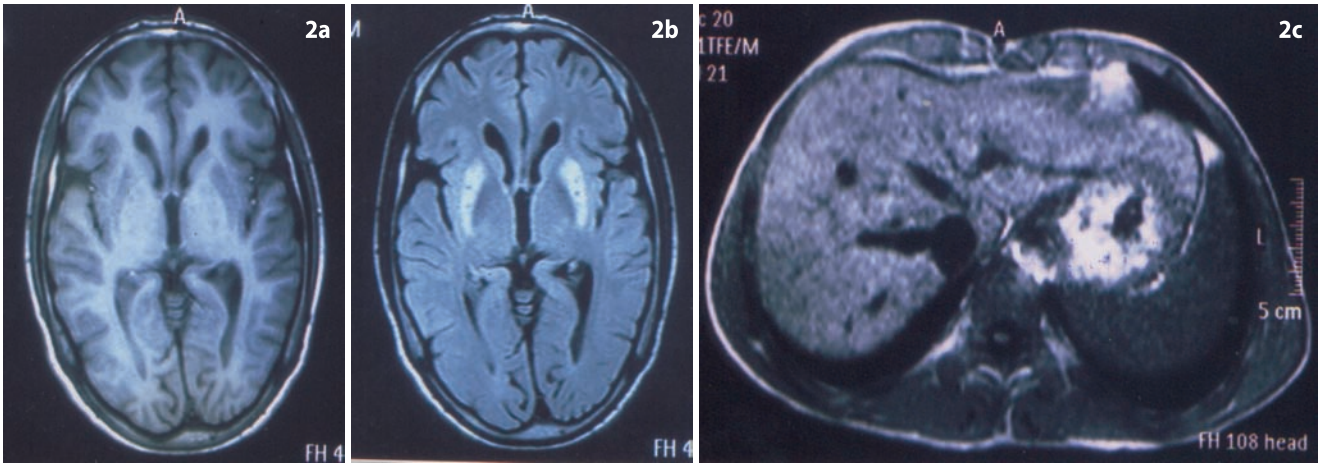

Fig. 2: *Magnetic resonance imaging* ***(2a)*** *T1W image showing hypointensities of bilateral basal ganglion;* ***(2b)*** *T2W image showing hyperintensities of basal ganglion;* ***(2c)*** *T1W image of liver showing hyperintensity of parenchyma.*

µg/dl). Serum ceruloplasmin levels were decreased to 11.10 mg/dl (N: 20 - 60 mg/dl) and serum copper to 54.92 µg/dl (N: 70 - 140 µg/dl). 24-hr urinary copper levels were 350 mcg/gm dry weight of liver. Serum uric acid levels were 1.0 mg% with normal 24-hr urine uric acid, amino acid, phosphorous, and protein levels. Slit lamp examination of eyes revealed golden brown Kayser-Fleisher rings on corneal periphery which were also seen with naked eyes. Ultrasound abdomen showed mild hepatomegaly with normal echotexture and portal vein diameter.

CECT head showed subtle hypodensities in bilateral basal ganglia. On MRI brain, wedge-shaped lesions isointense on T1W image and hyperintense on T2W/FLAIR image are seen involving bilateral putamen, thalami, midbrain, and pons, suggestive of heavy metal deposition gliosis. MRI of liver revealed increased signal intensity with changes suggestive of chronic liver disease. Liver biopsy showed mild inflammation with fibrosis without cirrhotic nodules. Despite normal liver function tests and without any symptoms, the patient had evidence of chronic liver disease on imaging and pathology. Based on clinical features, investigative profile, and characteristic MRI findings, a diagnosis of Wilson's disease was made. The patient was given therapy in the form of oral zinc and after 2 months follow-up, his urinary copper levels started declining.

Discussion

Wilson's disease is transmitted as an autosomal recessive trait. Neuropsychiatric Wilson's, as primary manifestation, is a rare presentation, in the order of 1 per 50,000 to 1 per 1,00,000 of the general population. The gene called ATP7B which is defective, codes for a membrane bound, copper binding ATPase. It causes reduced excretion of copper in bile and reduced incorporation of copper into ceruloplasmin, leading to accumulation of copper in various organs, viz, liver, kidney, brain and eyes[1].

Neurologic presentation tends to occur in the second or third decade, may be as early as 6 to 10 years of age. Most patients have hepatic involvement, often asymptomatic. Patient may present as movement disorders or rigid dystonia[2]. Movement disorders are relatively earlier in onset and include loss of fine motor control, tremor, and incoordination. Later, there may be pseudobulbar involvement resulting in dysphagia, dysarthria, and drooling of saliva. Parkinsonian features as mask-like facies, rigidity, and gait disturbance can also be seen. Psychiatric symptoms such as emotional lability, depression, and intellectual decline of faculties are rare, and seen in only 15% of patients. Rarely, patients may be severely agitated, restless, with delusive thoughts[3]. Our patient had depression, suicidal thoughts, and poor scholastic performance for the last 2 years. Kayser-Fleischer (K-F) rings are present in 95% of neurologic WD cases; but may be absent in 40 - 60% of patients with exclusively hepatic involvement and presymptomatic patients.

The patient's siblings were examined for KF rings, urinary copper levels, ceruloplasmin levels, but were found to be normal. Although genetic mutational analysis is the most reliable way to identify an affected sibling, it is not readily available in our country.

The diagnosis is virtually certain when there is a similar syndrome in a sibling or an extrapyramidal motor disorder is conjoined with corneal rings and liver disease. Neuropathology shows nerve cell loss, and some

degeneration of myelinated nerve fibers in lenticular nuclei, substantia nigra, and dentate nuclei with copper deposition. Total serum copper levels are reduced as serum ceruloplasmin levels are also reduced. The best marker is raised 24-hour urinary copper levels, which is also monitored as response to treatment[1]. MRI findings reflect the neuropathology with heavy metal deposition appearing as T2W hypointensities and neurodegenerative areas appearing as hyperintense on T2W images[4]. A classic finding on MRI is 'face of the giant panda' sign. A rare association of Wilson's disease can be Fanconi's syndrome[5]. This is characterised by aminoaciduria, phosphaturia, and uricosuria. In our patient, although serum uric acid levels were decreased, urinary excretion was found to be normal. Hypouricaemia is also an association with Wilson's disease due to reduced synthesis of uric acid in liver.

For neurologic WD, oral zinc is the treatment of choice. It reduces absorption of copper from gastrointestinal tract and may enhance its urinary excretion; does not cause neurological worsening. D-penicillamine is not used as it worsens neurologic symptoms. Ammonium tetrathio-molybdate is a new drug which also has been found to be effective. Until it is commercially available, zinc is recommended. Penicillamine and trientine should be avoided as they worsen neurological symptoms. Pregnant patients should be treated with zinc or trientine throughout pregnancy, but with tight copper level control, as copper deficiency can be teratogenic. Anticopper therapy must be lifelong. Neurologic and psychiatric improvement is seen in 6 and 24 months[6] of therapy. Symptomatic treatment for symptoms of muscle spasm, stiffness, and tremor may include anticholinergics, tizanidine, baclofen, levodopa, or clonazepam. A high degree of suspicion and early detection of WD is critical because early initiation of chelation therapy can prevent a catastrophic outcome.

To conclude, our case illustrates that neurological manifestations may be the initial presentation. Absence of family history and symptom free hepatic involvement may delay the diagnosis, but K-F rings are usually detected in majority of patients. Effective treatment modalities are now available and a high index of suspicion in diagnosing Wilson's in childhood helps improved outcome in patients detected early in the course of the disease.

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CASE REPORT

JIACM 2013; 14(3-4): 273-7

Unilateral ptosis and contralateral lid retraction – An unusual sign in recurrent attacks of ocular myasthenia gravis

Geeta A Khwaja, Amit Batla**, Meena Gupta***, Debashish Cowdhury*, Rajeev Ranjan***

Abstract

Ocular manifestations are an integral part of myasthena gravis (MG). Ptosis and diplopia are the initial complaint in around 75% cases, but eventually develop in 90% of all cases[1,2]. Ocular MG, in which weakness remains confined to the ocular muscles only, is encountered in up to 17% to 58% of all myasthenics[1]. Some less common or rare ocular signs like paradoxical reversal of ptosis, enhanced ptosis, total external ophthalmoplegia, internuclear ophthalmoplegia, chronic progressive external ophthalmoplegia and lid retraction contralateral to the ptotic eye, may also be observed in myasthenic patients[2,7]. Lid retraction is extremely rare in MG (4 out of 150 patients in a study by Kansu et al)[7] and may also be observed in patients with thyroid ophthalmopathy. MG occurs in fewer than 1% of dysthyroid patients but in patients with co-morbid disease the diagnosis, is often confounded by similar ocular signs[2]. Antibodies against the acetylcholine receptor are present in about 50-75% of patients with ocular MG[2]. If weakness remains limited to the ocular muscles after 2 years, there is a 90% likelihood that the disease will not generalise[1]. We report an unusual paradoxical ocular sign, with lid retraction contralateral to the ptotic eye in a patient with recurrent attacks of ocular MG and concomitant long-standing hypothyroidism, along with a brief review of literature with regards to ocular MG and its association with thyroid disorder.

Introduction

Ocular manifestations of myasthenia gravis (MG) are well defined and encountered in up to 90% cases. Unilateral ptosis with contralateral lid retraction is however an unusual and uncommon ocular sign and we report one such case with comorbid hypothyroidism and recurrent attacks of ocular MG.

Case history

A 64-years-old male on treatment for hypothyroidism (16 years), hypertension and diabetes mellitus (5 years), presented to us with a 10 days history of fluctuating unilateral ptosis of the right eye accompanied by simultaneous retraction of the left upper eye lid with widening of the left palpebral fissure. History of diurnal variation with worsening of the symptoms by evening and relative normalcy of eye signs on waking from sleep in the morning or after periods of rest during the day was present. Ptosis of one eye was always accompanied by retraction of the other eyelid. There was no history of diplopia, restriction of ocular movements, or visual impairment. There was no history facial, jaw, bulbar, neck, or limb muscle weakness, and no history of easy fatiguability.

There was history of a similar ocular attack, 2 years back, with spontaneous recovery within 10 days. Sixteen years back, at the time of being diagnosed as hypothyroid, he had developed significant intermittent diplopia, without accompanying ptosis or restriction of ocular movements or any other signs. Diplopia persisted for around 2 months and abated within one month of starting treatment with thyroxine (200 µg/day). The current attack had occurred within 6 months of reducing the thyroxine dosage to 100 µg/day by the patient himself.

General and systemic examination was normal. Higher mental functions were intact. On ocular examination the patient had near complete right-sided ptosis with simultaneous retraction of the left upper eyelid and widening of the left palpebral fissure (Figure 1). There was no restriction of ocular movements, diplopia, or facial weakness. Visual acuity and fundus examination was normal. Other cranial nerves were intact. There was no motor or sensory deficit. DTR were normal and plantars bilaterally flexor.

On investigation, haemogram, KFT, LFT, lipid profile, and serum electrolytes were in the normal range. Fasting blood sugar was 147 and post-parandial 248 mg/dl. TFT revealed a mildly elevated TSH (5.83 µIU/ml), but T3 (1.09 ng/ml) and T4 (8.20 µg/dl) were in the normal range. ECG and X-ray chest were normal. CT chest did not reveal any evidence of thymoma. Repetitive nerve stimulation did not reveal any evidence of decremental response in the facial (frontalis/nasalis) or limb (abductor pollcis brevis) muscles. Neostigmine test was positive for myasthenia gravis with near complete recovery of the ocular signs. Interestingly, reversal of the ocular signs with retraction of the ptotic eye and ptosis of the retracted eye was observed 20 minutes after intravenous injection of 1 mg neostigmine (Figure 2).

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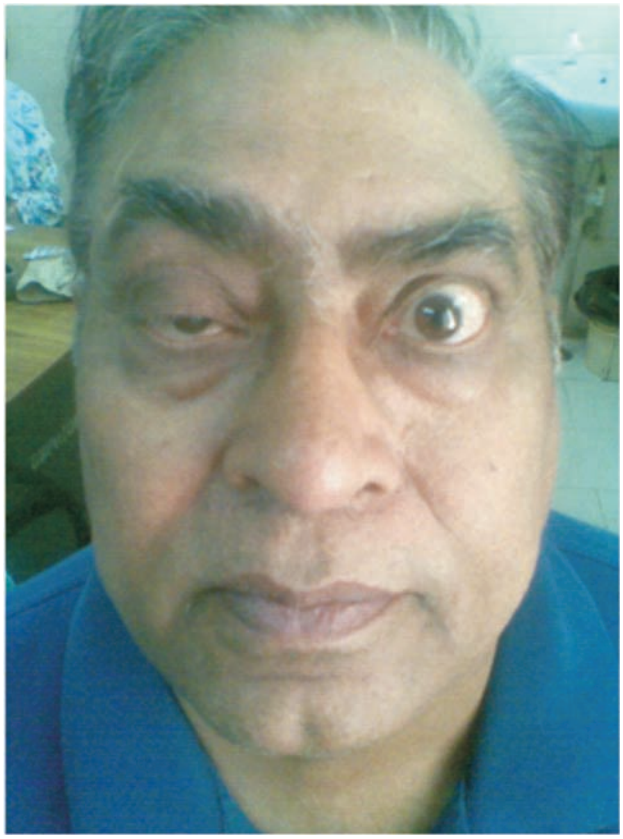

Fig. 1: *Pre-treatment photograph showing ptosis of the right eye and retraction of the left eyelid.*

Fig. 2: *Post-injection neostigmine photograph showing reversal of the ocular signs.*

This effect reverted back to the original status 2 hours post-injection. Anti-Ach receptor antibodies were positive in the serum. Testing for antithyroid antibodies was not done.

A diagnosis of recurrent attacks of ocular myasthenia gravis with underlying hypothyroidism was made. In view of the mildly elevated TSH level, the dosage of thyroxine was stepped up to the previous level of 200 µg/day. The ocular signs showed a good response to pyridostigmine (60 mg three times a day), and abated over the next one month.

Discussion

MG has a prevalence of around 20 per 100,000 in the US population[1]. The incidence varies widely from 1.7 to 10.4 per million, depending on the location of study[1]. Acquired myasthenia gravis (MG) is an antibody-mediated autoimmune disorder of transmission at the neuromuscular junction (NMJ). The occurrence of MG is influenced by sex and age: women are affected nearly three times more often than men during early adulthood (age <40 years)[1]. After 50 years of age, incidence is higher in men. Early-onset MG is usually defined as beginning before the age of 40 years[1]. Patients with late onset MG can present with ocular or generalised weakness, but typically have a more severe disease course compared with early-onset MG, and spontaneous remissions are rare. Myasthenic weakness that remains limited to the ocular muscles is termed ocular MG, and comprises 17% of all MG in white populations[1]. Ocular MG seems to be more common in Asian populations (up to 58% of all patients with MG), with a predilection for children[1]. Our patient presented with 3 attacks of late onset ocular MG spread over a span of 16 years. Differences in clinical presentation, age at onset, autoantibody profile, and the presence or absence of thymic pathology allow identification of several MG clinical subtypes. Appropriate recognition of these clinical subtypes helps to determine management strategies and prognosis.

Myasthenia gravis may affect virtually any striated muscle, including the facial, bulbar, trunk, and limb musculature, but the extra-ocular muscles are particularly susceptible. The two defining clinical characteristics of myasthenic weakness are "variability" and "fatiguability", in which the symptoms worsen with exertion and improve with rest. A diurnal pattern with worse symptoms in the evening is not uncommon. Combined patterns of weakness of the extra-ocular muscles, levator palpebrae superioris, and orbicularis oculi are highly indicative of myasthenia. Ptosis and diplopia are the initial complaint in 75%, and eventually develop in 90% of all myasthenic patients[2]. Also, in a substantial minority, the manifestations of the disease continue to be limited to the eyes over many years. In one survey of patients with ocular myasthenia, 10% had ptosis only, 90%

had a combination of ptosis and diplopia due to ocular weakness, while 25% had added weakness of the orbicularis oculi[3]. Thus, awareness of the ocular manifestations of this disease is critical to clinical practice. Ptosis may be unilateral or bilateral, and is usually asymmetric initially. It is typically variable, with prominent fatiguability, sometimes not apparent on awakening, only to develop and worsen over the course of the day, and usually worsens with repeated eye opening or prolonged up-gaze. Our patient also presented with a history of fluctuating, unilateral ptosis with diurnal variation in two of the attacks and isolated diplopia in one attack. Diplopia is the second most common manifestation of ocular myasthenia. Although any muscle may be affected, the medial rectus, inferior rectus, and superior oblique are more commonly affected[2]. Any pattern of incomitant strabismus may develop, from single muscle paresis to total external ophthalmoplegia. It can mimic peripheral nerve palsies, such as IV, VI, and partial III nerve palsy, and also central disorders of gaze, including unilateral or bilateral internuclear ophthalmoplegia, one-and-a-half syndromes and double elevator palsy[2]. When severe and diffuse, ocular myasthenia gravis may be hard to distinguish from chronic progressive external ophthalmoplegia (CPEO). Bell's phenomenon, elevation of the eyes on forced eyelid closure, may also be diminished or absent in myasthenia gravis[2].

Some uncommon or rare ocular signs may also be observed in myasthenic patients. *Paradoxical reversal of ptosis* has been described, in which ptosis switches eyes during the course of a day, as a function of rest, or administration of edrophonium[4]. While this may simply reflect the moment-to-moment variability of the disease, the explanation of reversal with edrophonium is still not clear. Secondary adaptive features may also produce certain signs. As with other cause of ptosis, a lid droop may appear mild because of partial compensation: the true extent of ptosis can be revealed by covering the ptotic eye and observing the gradual increase in ptosis behind the cover over several minutes[2]. *Enhanced ptosis* is a related sign in which manual lifting of a ptotic eyelid, by eliminating the need for compensation, causes the other apparently normal eye to develop ptosis, showing that the lid dysfunction is actually bilateral[5]. This second-eye ptosis had been masked because the central compensatory increase in innervation directed at overcoming the more severe ptosis in the first eye is distributed to both eyes by Hering's law[6]. Manual elevation of one eyelid reduces the effort required to raise that eyelid and thus according to Hering's law, less effort is also exerted by the contralateral levator muscle, and that eyelid becomes more ptotic. Enhancement of ptosis is not pathognomonic for myasthenia gravis, as it can be seen in patients with other causes of congenital and acquired ptosis, but in patients with appropriate history, it is highly suggestive of myasthenia gravis.

Lid retraction contralateral to the ptotic eye has also been described and may reflect a compensatory or secondary adaptive effect by the central nervous system[2,7]. In response to unilateral or asymmetric ptosis, the system increases innervation to both lids (Hering's law): the resulting lid retraction on the less affected side may appear more prominent than the ptosis on the weaker side[2,7]. As with enhancement of ptosis, manual lifting of the ptotic lid will allow the opposite retracted lid to return to a more normal position, revealing the compensatory origin of the retraction. Our patient also presented with this uncommon sign.

Causes of eyelid retraction can be classified as neurogenic, myogenic, and mechanistic, and myasthenia gravis has been listed as one of the myogenic causes of the same but is extremely rare[2,8]. In a study by Kansu *et al*, 4 out of 150 patients with myasthenia gravis had upper lid retraction[7]. Of these, only two had apparent ptosis in the contralateral eye. Three patients developed this paradoxical sign during medical treatment and after thymectomy. Hering's law of equal innervation does not adequately explain this phenomenon, and the possibility of cholinergic overstimulation in neuromuscular transmission is raised. Occasionally, the diagnostic impression in a myasthenic patient is led astray because of apparent *lid retraction* only, rather than ptosis. Sometimes this reflects co-existent thyroid ophthalmopathy, most frequently Graves ophthalmopathy. Lohman *et al* have reported unilateral lid retraction secondary to a contralateral ptosis in a case of dysthyroid ophthalmopathy[9]. Yamazaki *et al* have reported pseudo-internuclear ophthalmoplegia as a sign of overlapping myasthenia gravis in a patient with intractable hypothyroidism[10]. Myasthenia gravis (MG) occurs in fewer than 1% of dysthyroid patients[2]. Our patient had an underlying hypothyroidism of 16 years duration that was brought to the forefront by an attack of ocular MG, that abated within one month of initiating treatment with thyroxine. Also, the third attack of ocular MG in our case was precipitated by reduction of thyroxine dosage to one half of the previous dose and the TSH levels were also mildly elevated at the time of this attack. MG and hypothyroidism share some features, principally weakness and fatiguability of voluntary muscles. Thus, once a diagnosis of weakness and fatiguability due to hypothyroidism is established, a diagnostic pitfall overlooking an additional muscle weakness caused by a co-occurrence of MG can occur, as happened with our case in the first attack. Moreover, treatment of the hypothyroid state itself, may have a positive impact on myasthenic

weakness, as was observed in our case also.

Acquired myasthenia, is caused by pathogenic autoantibodies directed against the nicotinic acetylcholine receptor (AChR) in the motor end-plate of striated muscles in most cases, as was the case with our patient. Antibodies against the acetylcholine receptor are present in 80 - 90% of patients with generalised and in about 50 - 75% of patients with ocular myasthenia gravis[2]. In others, non-AChR components of the post-synaptic muscle endplate, such as the muscle-specific receptor tyrosine kinase (MUSK), might serve as targets for the autoimmune attack[2]. Whereas patients with anti-MUSK antibodies can have presentations similar to anti-AChR-positive MG, they commonly have atypical clinical features, such as selective facial, bulbar, neck, and respiratory muscle weakness and marked muscle atrophy, with relative sparing of ocular muscles[1]. Anti-MUSK antibodies are rarely found in ocular MG. In addition to anti-AChR antibodies, patients with late onset MG can have antibodies directed against striated muscle proteins such as titin and the ryanodine receptor[1]. The presence of these anti-muscle antibodies, particularly anti-ryanodine receptor antibodies, has been associated with more severe, generalised, or predominantly oropharyngeal weakness, and frequent myasthenic crises[1].

The precise origin of the autoimmune response in MG is not known, but genetic predisposition and abnormalities of the thymus gland play a role. Thymic hyperplasia, characterised by infiltration of the thymus with lymphocytes and plasma cells, is found in around 65 - 70% cases[2]. Between 7 - 26% cases have thymoma, which can be detected by CT scan of the thorax[2]. There was no evidence of thymoma in our case. Thymoma-associated MG is equally common in men and women, and can occur at any age, with peak onset at the age of 50 years. Clinical presentations tend to be more severe, with progressive generalised and oropharyngeal weakness. Mortality rates are higher and morbidity tends to be more severe in such patients. With rare exceptions, MG patients with thymoma have high titres of anti-AChR antibodies, and they usually also have antibodies against titin[1]. In about 40% of these patients, antibodies to MUSK are also found[1]. Patients with MG who lack both anti-AChR and anti- MUSK antibodies (so-called seronegative MG) are clinically heterogeneous and can have purely ocular, mild generalised, or severe generalised disease. These patients are essentially indistinguishable from patients with anti-AChR-positive MG in terms of clinical features, pharmacological treatment response, and even thymic abnormalities in some cases[1].

The immunopathogenesis of ocular MG is likely to be similar to that of early or late onset generalised MG but ocular myasthenics tend to have lower titres of antibodies. Moreover, actual antibody titres, have poor correlation with the disease severity and higher titres do not necessarily predict generalisation[1,2]. Antibodies in ocular myasthenia may also differ qualitatively from those in generalised myasthenia: sera from such patients are more likely to be positive when tested against acetylcholine receptor from ocular muscle than against those from limb muscle[2]. The predilection of myasthenia for the ocular muscles may be related to differences between limb and extraocular muscles in either physiological function or antigenicity. It is possible that ocular myasthenia simply reflects less severe disease. Another possibility is that there are differences between extra-ocular and limb acetylcholine receptors and enhanced susceptibility of extraocular muscles to MG might result from differences in NMJ morphology and physiology. Extraocular muscles have less prominent synaptic folds, fewer postsynaptic AChRs, and smaller motor units, and are subject to high firing frequencies[1]. Another possibly relevant factor is low expression of complement regulators in extraocular muscles, which might make them more vulnerable to complement mediated damage[1].

Autoimmune thyroid disease may be associated with myasthenia. Either hyper- or hypothyroidism may precede or follow the development of myasthenia. In our case, the first attack of ocular MG led to a diagnosis of hypothyroidism and abated with treatment of the same. Twenty-five per cent of those with normal levels of thyroid hormone will have antithyroid antibodies[2]. Conversely, 8% of patients with Graves' disease have antibodies against the acetylcholine receptor[2]. Other autoimmune diseases including rheumatoid arthritis, thyroiditis, polymyositis, pernicious anaemia, and thrombocytopenia are occasionally found[2].

Tests to confirm the diagnosis of MG include edrophonium challenge, repetitive nerve stimulation (RNS), single-fibre electromyography (EMG), and antibody assay: all are less sensitive for ocular myasthenia than for generalised myasthenia. In our case there was no decremental response on RNS of facial / limb muscles, but neostigmine test was positive and anti-Ach receptor antibodies were also detected in the serum. The reversal of ocular signs: retraction of ptotic eye and ptosis of the retracted eye following injection neostigmine, is another paradoxical sign that was observed in our case. *Paradoxical reversal of ptosis*, in which ptosis switches eyes as a function of rest, or administration of edrophonium has been described as discussed, but as to why the ptotic eye became retracted following injection neostigmine in our case, is difficult to explain[4].

Treatment consists of symptomatic use of

acetylcholinesterase inhibitors and immunosuppression with steroids or azathioprine. Acetylcholinesterase inhibitors such as pyridostigmine and neostigmine are the mainstays of *symptomatic treatment* and benefit around 90% of the cases although they are less effective for diplopia than ptosis, and the benefit may be relatively mild in around 50% cases[2]. Anticholinesterase medications provide only symptomatic relief and do not improve the outlook for ocular myasthenia. Our patient however, showed a good clinical response to pyridostigmine.

Whether predisolone, other immunosuppression or thymectomy, alters the likelihood of generalisation is not yet entirely clear. Between 50% and 70% of patients with ocular myasthenia will eventually develop generalised disease and two retrospective reviews have suggested that steroids and azathioprine may reduce the rate of generalisation by as much as 75%[2]. *Immunosuppression* with low-dose, alternate-day prednisolone is helpful in almost 90% of patients with ocular myasthenia and improves diplopia in about 75%, with minimal side effects[2]. Initiation of steroid therapy traditionally involves higher dose daily regimens and can be associated with transient worsening of myasthenic weakness in the first few weeks. Azathioprine is widely used as a steroid-sparing immunosuppressant in the long-term treatment of myasthenia. There is little data on its use in ocular myasthenia; however, its combination with low-dose prednisolone was helpful in 91% of a small sample of 23 patients[11]. Other immunosuppressant drugs such as cyclosporine are more toxic and there is even less data on their use for ocular myasthenia. Our patient did not qualify for immunosuppressive therapy because of the short duration of the attacks.

Thymectomy is indicated in all patients with thymoma and generalised myasthenia. It is helpful in inducing remission in 10 - 30%, and improvement in up to 80% of patients with generalised myasthenia[2]. The role of thymectomy in ocular myasthenia remains unclear. Whether it should be routinely used in patients with pure ocular myasthenia, with or without suspected thymic hyperplasia, is more controversial. Most neurologists limit its use in ocular myasthenia to those with severe signs. However, the evidence is mixed. Some claim that it offers no benefit, while others claim significant improvement in 80% of patients who fail to respond or relapse with drug therapy. Available data are too scant to show whether thymectomy adds any prognostic advantage. Short-term immunomodulation can be achieved with plasmapheresis and intravenous immunoglobulin. These are usually reserved for severe systemic weakness and crisis, and are seldom required for ocular myasthenia.

In a patient with signs limited to the ocular muscles only, a key issue is the likelihood of developing generalised myasthenia. Purely ocular myasthenia tends to start at a slightly later age than generalised myasthenia and is more common in men, as was the case with our patient. Disease progression to generalised weakness usually occurs within 2 years of disease onset[1]. If weakness remains limited to the ocular muscles after 2 years, there is a 90% likelihood that the disease will not generalise, a phenomenon that was observed in our case also[1]. A study of nearly 1,500 patients showed that about 50% presented with strictly ocular involvement. Of this group with ocular myasthenia, about 30% did not generalise over a mean of 17 years of follow-up; among the 70% who progressed, 94% did so within the first 3 years[12]. Similar findings were reported in another study, with 50% of patients with ocular myasthenia developing generalised disease, and 80% of these doing so within 2 years of diagnosis[13]. Ten per cent actually achieved complete remission, although remission at a later date remained possible[13]. Development of generalised myasthenia after 3 years can occur, but it does so at a slower rate[2].

In conclusion, we report an unusual paradoxical ocular sign in a patient with concomitant hypothyroidism and recurrent attacks of ocular MG, both of which can have similar ocular manifestations, thereby confounding the diagnosis. It is common for patients with ocular myasthenia to receive several misdiagnoses. Awareness and attention to historical details and proficiency in detecting subtle myasthenic eye signs are important for an early correct diagnosis and management.

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CASE REPORT

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Intermittent left bundle branch block – A diagnostic dilemma

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Abstract

Rate dependent LBBB is a well recognised electrocardiographic entity. However, the clinical significance of rate dependent or intermittent LBBB is still uncertain. Here we report a middle-aged diabetic lady with intermittent LBBB as a result of acute coronary syndrome.

Key words: Intermittent LBBB, coronary artery disease.

Introduction

Bundle branch block (BBB) may occur in a variety of conditions and may be chronic or intermittent in nature. Rate-related LBBB exhibits a wide spectrum of clinical association; however its significance is yet to be made with certainty. LBBB is often a marker of one of the four underlying conditions associated with increased cardiovascular morbidity and mortality – coronary artery disease (CAD), hypertensive heart disease, aortic valve disease, and cardiomyopathy. Rate-dependent LBBB likewise, may be a manifestation of CAD or myocardial dysfunction, but it can even occur with normal coronaries. Here we report a case of intermittent LBBB who posed diagnostic dilemma and difficulties in decision making.

Case history

A 45-year-old diabetic woman was brought to the emergency department of our hospital with the chief complaint of intermittent chest pain at rest for the last 6 hours which was retrosternal in location, lasting nearly 15 - 20 minutes during each episode. It was associated with sweating, palpitation, and dyspnoea and a feeling of extreme distress. There was no nausea, vomiting, or any radiation of the chest pain. There was no history of fever, orthopnoea, syncope, or peripheral oedema. Past history of similar chest discomfort was absent. After a period of 15 - 20 minutes there was complete resolution of the chest pain and other associated symptoms, but only to recur again.

On clinical examination, she looked pale and anxious during the attack and her pulse rate rose from 78 to 130 bpm, and blood pressure rose from 146/84 to 190/116 mm Hg. She was sweaty, tachypnoeic, her JVP was normal, and there was no pedal oedema. On auscultation, S_1 & S_2 was normal and without any murmur or rub.

Upon resolution of the episodic chest pain she became completely comfortable. Her pulse rate and blood pressure returned to baseline.

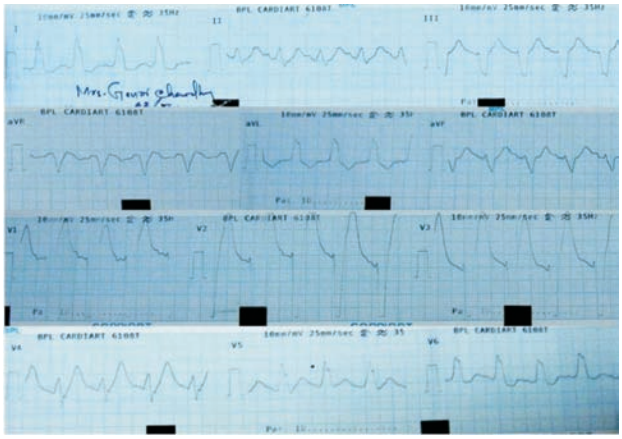

Fig.1: *ECG showing complete LBBB during chest pain.*

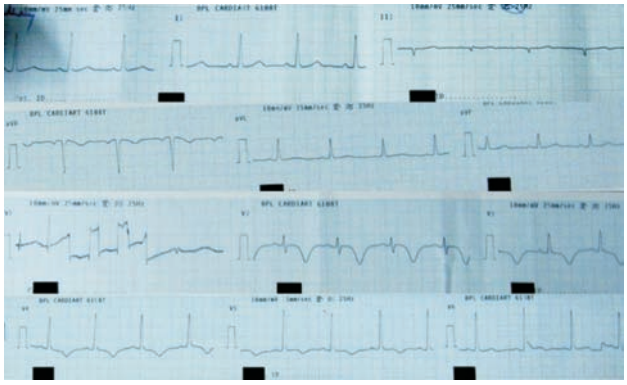

Fig. 2: *ECG reverted to normal sinus rhythm with T wave inversion.*

She was subjected to standard baseline investigations and was shifted to ICCU for continuous cardiac monitoring. Her 12 lead electrocardiogram revealed complete LBBB with a HR of >100 bpm during the episode of chest pain (Fig. 1). This LBBB reverted to normal sinus rhythm with T inversion in leads V_1 – V_4 as the pain subsided and heart

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rate touched the normal range (Fig. 2). During the hospital stay this intermittent LBBB reappeared on several occasions with recurrence of chest pain.

On laboratory evaluation, her Trop-I was negative, blood sugar was 340 mg/dl, creatinine was 1 mg/dl, CPK-MB was 16 IU; serum lipids showed cholesterol - 220 mg/dl, triglycerides - 156 mg/dl, HDL - 44 mg/dl, LDL - 151 mg/dl, VLDL - 31 mg/dl.

Her chest X-ray was normal and echocardiography showed concentric left ventricular hypertrophy with normal LV function. Trop-I was repeated at 6 hours and 12 hours but all turned out to be negative. She was put on IV insulin, and conservative management for acute coronary syndrome. Because of the repeated history of ongoing angina with medical management, she was sent for a coronary angiogram which revealed 80% occlusion in proximal LAD for which PTCA with stenting to LAD was performed.

Discussion

The phenomenon of intermittent LBBB is usually rate dependent. The presence or absence of LBBB depends on slight differences in heart rate which are often below the threshold of tachycardia and is not constant over the time. The heart rate at which bundle branch block (BBB) occurs is known as critical heart rate[1,2]. This rate-dependant BBB may also be tachycardia or bradycardia dependant.

We report here a patient of intermittent LBBB presenting with acute coronary syndrome who posed a diagnostic dilemma. Recognition of this rate-dependent LBBB is of paramount importance because it needs to be distinguished from a patient with new-onset LBBB with ischaemic chest pain, which forms an indication for thrombolytic therapy[3]. The critical heart rate at which normal sinus rhythm converts to LBBB is often higher than the rate at which it disappears. Surawicz *et al*[4] revealed that patients of intermittent LBBB may have transient T wave inversion when ECG reverts to normal sinus rhythm because of repolarisation abnormality. This abnormal T wave may be pronounced and consideration must be made that it could reflect critical LAD occlusion. Before the advent of coronary angiography, rate-dependent BBB was considered to result from coronary artery disease[5]. However, this is not always true.

Wayne *et al*[6] suggested that exercise-induced LBBB is almost always associated with demonstrable cardiac abnormality – mostly occlusive coronary disease. Whereas Vieweg *et al*[7] reported intermittent LBBB in patients with normal coronary arteries. Similarly, Virtanen *et al*[8] also found rate-dependent LBBB in patients with chest pain having normal coronary arteriogram. Myocardial perfusion imaging revealed reversible perfusion defects in the absence of stenotic CAD in patients with LBBB and angina pectoris[9].

However, one randomised controlled study of patients with intermittent LBBB suggests that there exists a relationship between intermittent LBBB and acute coronary syndrome, and that it may be an independent prognostic marker for CAD. Exercise-induced LBBB has also been shown to be a strong predictor for major cardiac events[10]. It is postulated that patients who present with typical anginal chest pain and rate-dependent LBBB at a heart rate of < 125/min is usually indicative of ischaemic heart disease, whereas those who develop LBBB at heart rate of >125/min are generally cases of non CAD[11].

Recognition of this electrocardiographic entity is of importance since it could mislead the emergency physician and may lead to errors in decision making while dealing with a case of chest pain with new-onset or intermittent LBBB. Serial ECGs may help to distinguish the two abnormalities here.

Though the lone presence of intermittent LBBB may not always be considered to reflect acute ischaemia, our case report here highlights that it is imperative for the attending physician to keep a high index of suspicion for coronary artery disease even with negative cardiac biomarkers.

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CASE REPORT

JIACM 2013; 14(3-4): 280-3

PUO as a presenting feature of hypercoagulable state

Ashok Duggal, Sachin Khurana***

Abstract

PUO as a presenting feature is rare in hypercoagulable state and in such cases, vascular examination along with cardiac examination is of paramount importance. A case of extensive thrombosis of arterial system along with venous and cardiac involvement presenting as PUO due to multifactorial hypercoagubility is being presented.

Introduction

A hypercoagulable state results in arterial as well as venous thrombosis. Most common congenital causes are hyperactivity of procoagulants (Type II) that is factor V Leiden mutation and prothrombin mutation (G20210A, 5'UTR) while most common acquired causes are antiphospholipid syndrome (aPL) and heparin-induced thrombocytopenia. The patient in discussion presented with PUO along with arterial and venous thrombosis having dual pathogenesis as heterozygous factor V Leiden mutation as well as antiphospholipid antibodies. The antiphospholipid syndrome is considered secondary when it occurs in the presence of systemic lupus erythematosus (SLE) or other major autoimmune conditions, and primary when it occurs in their absence. The majority of the thrombotic events affect the deep venous system of the lower limbs and arterial thrombosis predominates in the cerebral territory, but thromboembolism can involve almost any portion of the arterial or venous circulations. A case of extensive thrombosis of arterial system involving brachiocephalic trunk, carotid, and aorto-iliac arteries along with features of cerebral thrombosis and lupus endocarditis is described. Factor V Leiden which is reported with venous thrombosis but very rare with arterial thrombosis

Case report

A 50-year-old male presented mainly with mild-to-moderate degree of fever off and on since three months for which the patient got admitted in a private hospital where he was diagnosed as chronic rheumatic heart disease with MS with SABE and thromboembolic phenomenon resulting in right-sided hemiparesis, and subsequently put on antibiotics though the culture was negative. He remained admitted there for 15 days, but fever did not subside, and finally he shifted to our institution.

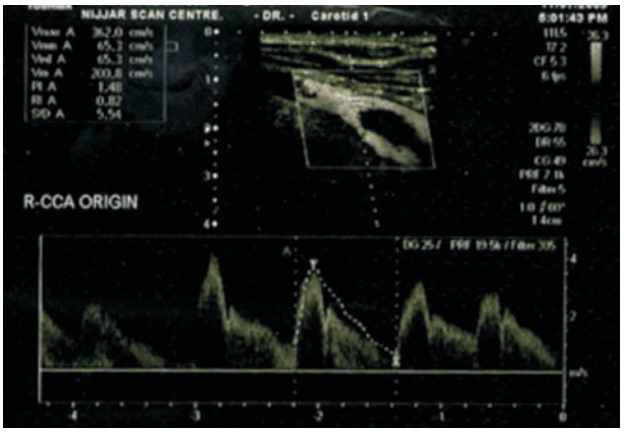

Fig. 1: *Thrombus in the right common carotid artery.*

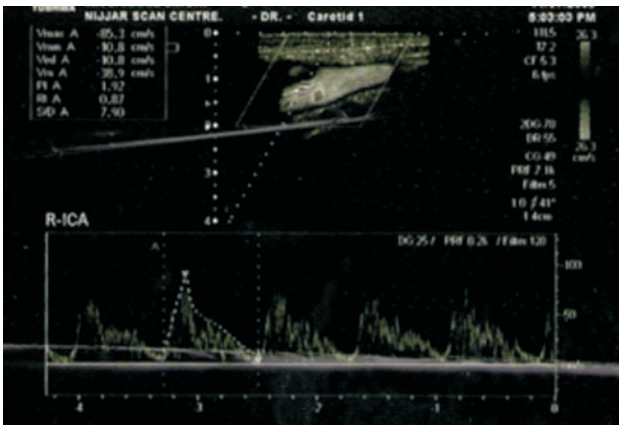

Fig. 2: *Thrombus in the right internal carotid artery.*

The patient had weakness of the right half of his body two months back without any history of loss of consciousness, headache, or nausea/vomiting associated with the episode. There was past h/o similar type weakness one year back which improved within two days. There was no prior history of hypertension, palpitations, MI; no h/o bleeding from any site. Also, there was no history of such an event in any of his family members.

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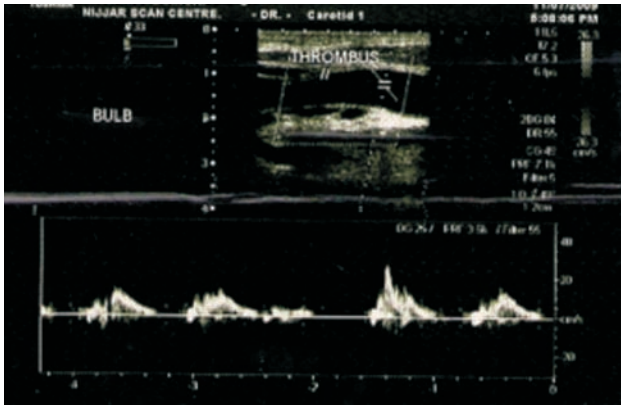

Fig. 3: *Thrombus in the bulb.*

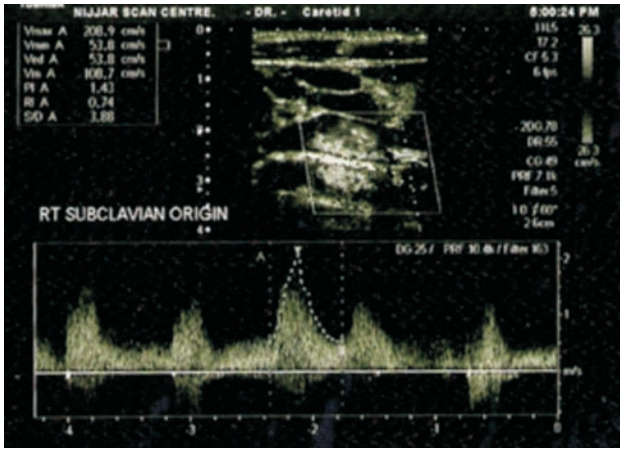

Fig. 4: *Thrombus in the right subclavian origin.*

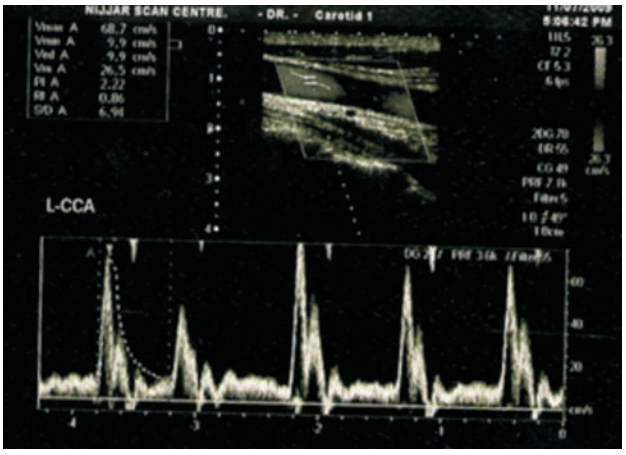

Fig. 5: *Thrombus in the left common carotid artery (CCA).*

On examination, his BP was 110/70 mm in the left arm, but in the right arm BP was not recordable. The right radial pulse was not palpable, and the left radial pulse was of poor volume, 86/min and regular. Temp was 100.4°, RR 20/min. Patient had mild anaemia; but no oedema, cyanosis, and jaundice. No petechial spots were seen.

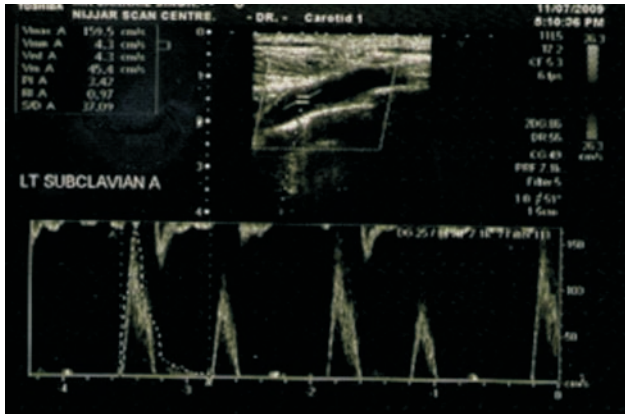

Fig 6: *Thrombus in the left subclavian artery.*

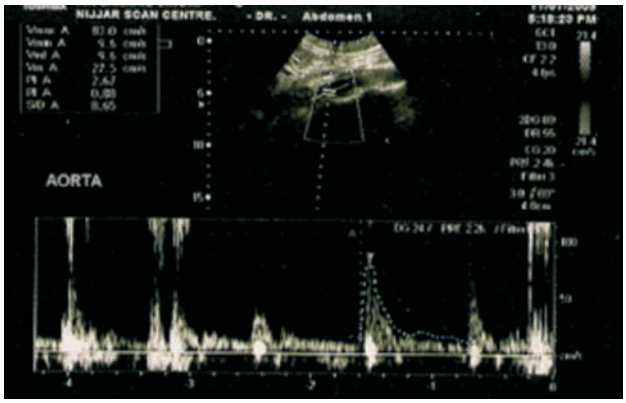

Fig. 7: *Thrombus in the aorta.*

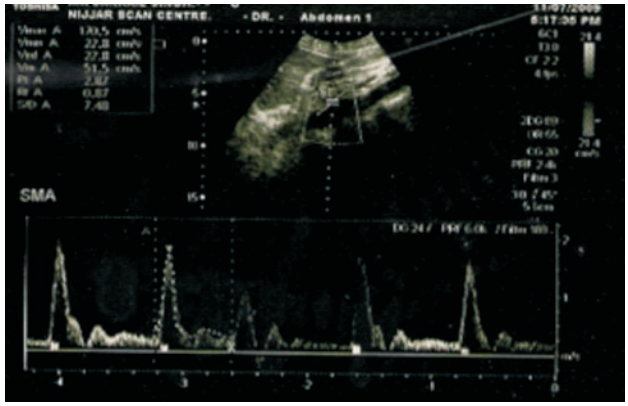

Fig. 8: *Thrombus in superior mesenteric artery (SMA).*

Neurological examination revealed normal higher mental functions and right-sided UMN facial palsy with no evidence of any other cranial nerve involvement. Power was grade 0/5 in both right upper and lower limbs. Deep tendon reflexes on the right side were brisk with plantar upgoing.

Examination of blood vessels showed a weak carotid along with thrill and absent radial on right side as well as weak carotid, radial on the left side. A systolic bruit was audible over the in right carotid artery. Femorals were weak on both sides along with absent dorsalis pedis. CVS

examination revealed grade 3 diastolic murmur along with grade 2 systolic murmur in the mitral area.

Laboratory investigations were as follows: Hb – 11.6 gm/dl, TLC – 10,400/mm^3, platelet count 280,000/mm^3, PTI-97%, aPTT – 28 sec, ESR 25mm in 1st hour; lipidogram: total cholesterol – 139 mg%, triglycerides – 125 mg%, HDL – 45 mg%. Serological testing was negative for SLE. Renal and hepatic function tests were within normal limits.

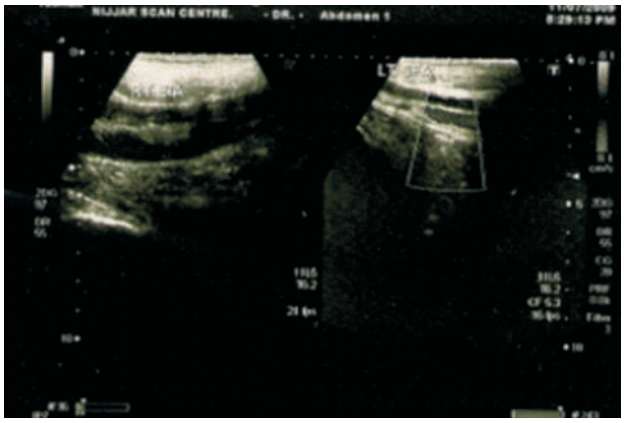

Fig. 9: *Thrombus in right external iliac artery (EIA) and superficial femoral artery (SFA).*

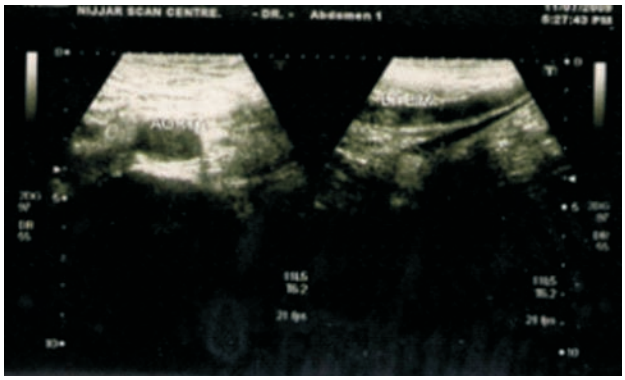

Fig 10: *Thrombus in aorta and left external iliac vein (EIV).*

CT scan head showed chronic lacunar infarcts seen in left internal capsule and lentiform nucleus along with chronic ischaemic changes and diffuse cortical atrophy.

Echocardiography revealed vegetations on thickened mitral cusps with restricted movements and also a few vegetations on aortic cusps. Doppler study of arterial and venous system showed thrombus in the brachio-cephalic trunk with extension into subclavian and common carotid arteries with compromised distal flow. Thrombus was seen in left ICA with complete occlusion; also, thrombus was seen in distal abdominal aorta with extension into iliac arteries on both sides with compromised flow in femoral arteries. The thrombosis was also seen in both external iliac veins. IgG and IgM cardiolipin antibody titres were in the intermediate range. Patient was also found to be heterozygous for factor 5 Leiden polymorphism. Patient was put initially on LMWH along oral anticoagulants and subsequently on oral coagulants only, maintaining INR between 2 and 3. Patient responded well to treatment whereby fever subsided, right radial pulse became palpable, and right carotid pulsations improved, resulting in gradual disappearance of carotid bruit along with improvement of femoral pulsations on both sides. This improvement persisted after one month follow up with further improvement in palpability of left carotid and left radial.

Discussion

Although very rare, primary antiphospholipid syndrome and thrombosis may present with PUO and diagnostic difficulties may delay the establishment of diagnosis. Prolonged fever as the sole manifestation of thrombosis is rather rare[1]. Kazmer's *et al* described fever in 16 out of 175 (9.1%) patients with deep vein thrombosis defined as temperature of $\leq 100^0F$[2].

The disorder is termed as primary if not associated with any other autoimmune condition, and secondary in the presence of such disorders. The genesis of the antibodies in this disorder and even their antigenic specificities are not well established. The disorder is generally considered to fall into the category of "autoimmune" conditions. The usual age of patients at the time of presentation with thrombosis is approximately 35 to 45 years[3] with the disease rarely presenting after age 60 years[4]. Patients may present with spontaneous venous and/or arterial thrombosis or embolism, which may involve any site in the vasculature. The syndrome should be especially suspected when unusual sites are involved or when a patient experiences recurrent thromboses with no other cause[5]. In one study of patients with radiologic evidence of thrombosis, 59 per cent had thrombi limited to the venous circulation, 28 per cent had solely arterial thromboses, and 13 per cent had both types of events[5]. Aortic or aortoiliac disease has been very rarely reported in the literature[6]. Elevated levels of aCL antibodies, whether high or low titre, were significantly associated with both myocardial infarction and cerebral stroke. Some patients with venous thrombosis, but generally not with arterial thrombosis[7], have concurrent genetic thrombophilic conditions such as heterozygosity for the factor V Leiden polymorphism[7,8,9,10].

Valvulopathy includes leaflet thickening, vegetations, regurgitation, and stenosis[11]. The mitral valve is mainly affected, followed by the aortic valve[12]. aPL syndrome valvular lesions consist mainly of superficial or intravalvular fibrin deposits in association with variable

degrees of vascular proliferation, fibroblast influx, fibrosis, and calcification. These conditions result in valve thickening, fusion, and rigidity, sometimes leading to functional abnormalities.

Other manifestations include pregnancy losses, thrombocytopenia, stroke, cerebral vein thrombosis, livedo reticularis, CAD, valvular heart disease, kidney disease, retinal disease, pulmonary hypertension, atherosclerosis, adrenal failure, haemorrhagic adrenal infarction, gastrointestinal manifestations, sensorineural hearing loss catastrophic antiphospholipid syndrome with microangiopathy

Three hypotheses have been presented to explain how aPL induces thrombosis. These include (a) endothelial cell activation; (b) oxidant-mediated vascular injury; and (c) interference with the function of phospholipid-binding proteins in regulating coagulation[13].

In our case, the patient was having arterial as well as venous thrombosis with cardiolipin antibodies in the intermediate range but additionally patient was heterozygous for Leiden V mutation indicating multifactorial hypercoagulabilty. We could not get prothrobin G20210A mutation done due to paucity of funds. Takayasu's disease was also considered but ruled-out due to presence of venous thrombosis in iliac veins and abnormal lab. parameters.

In patients with combined endocarditis and anti-phospholipid antibodies, anticoagulation therapy with warfarin is indicated due to high risk of valvular thrombus formation and subsequent embolisation. Experimental therapies for aPL syndrome include specific antiidiotypic or anti-CD4 antibodies, IL-3, ciprofloxacin or bromocriptine, and bone marrow transplantation[14]. Other new pharmacologic strategies under consideration but still unproved include statins, angiotensin-converting enzyme inhibitors to inhibit monocyte tissue factor expression, a β_2GPI-specific B cell tolerogen known as L J P 1082, and oral direct thrombin inhibitors.

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"No one is so old as to think that he cannot live one more year."

– Cicero.

SHORT COMMUNICATION

JIACM 2013; 14(3-4): 284-6

Cutaneous manifestations in cases of pulmonary tuberculosis: A clinical profile

HM Kansal, Shitij Goel***

Abstract

Primary pulmonary tuberculosis (TB) occurs soon after the initial infection with tuberculous bacilli while post-primary tuberculosis, also termed adult type TB may result from endogenous reactivation of distant latent infection or recent infection. Skin manifestations in tuberculosis may be due to direct involvement like lupus vulgaris, scrofuloderma, etc., or indirectly like tuberculids. Drug reactions like acneform eruptions, pruritus, xerosis or uncommonly Steven-Johnson syndrome etc may also occur due to anti-tuberculosis drugs. A total of 120 patients of pulmonary tuberculosis were screened for cutaneous manifestations, if any. In 30 patients we could find manifestations. Most common manifestations were acneform eruptions, pruritus, and skin xerosis. Less common were scrofuloderma and lupus vulgaris. One case of herpes zoster with pulmonary tuberculosis was also found.

Introduction

Tuberculosis is a global health problem[1]. Pulmonary tuberculosis (TB), as we know, is an infection of lungs caused by the rod-shaped, non-spore forming and aerobic bacterium *Mycobacterium tuberculosis*. The risk of developing disease after being infected depends upon an individual's immunological and non-immunological defenses and level of cell-mediated immunity[2]. Primary pulmonary tuberculosis occurs soon after the initial infection with tuberculous bacilli. Post-primary tuberculosis, also termed adult type TB, may result from endogenous reactivation of distant latent infection or recent infection. Extent of lung parenchymal involvement varies from small infiltrates to extensive cavitation[2].

Skin being the largest organ of body is affected commonly in any systemic condition. Cutaneous manifestations in tuberculosis will be either due to tuberculosis infection or otherwise.

Cutaneous tuberculosis can be classified as under[3]:

1) Exogenous source – Tuberculous chancre, warty TB, lupus vulgaris.
2) Endogenous source – Scrofuloderma, orificial TB, lupus vulgaris, tuberculous gumma, miliary TB of skin.
3) Tuberculids – Micropapular, papular, nodular.

Common anti-tuberculous drugs used in TB are isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin[4]. Use of these drugs can lead to various cutaneous drug reactions. Isoniazid has been frequently reported as a cause of acneform eruptions[5,6], while lichenoid eruptions, maculo- papular rash and others have been reported less commonly[7].

Tuberculosis-associated adverse drug reactions (ADRs) result in an interruption and change of treatment, both impacting on treatment failure, the development of drug resistance, relapse, and the transmission of disease[4].

Material and methods

Our study was conducted at the department of pulmonary medicine and department of dermatology of SMS & R and Sharda Hospital.

Inclusion criteria

All the patients who were diagnosed with pulmonary tuberculosis consecutively or were in the follow-up of the outpatient department of pulmonary medicine were screened for any skin complaint, and if found, were evaluated by a dermatologist for diagnosis and treatment.

- Only those patients with skin manifestations, which could have been directly or indirectly attributed to pulmonary tuberculosis or anti-tuberculosis drugs were included in this study.

Exclusion criteria

- Patients with pre-existing skin conditions, before diagnosis of TB, were not included.
- Patients with co-existing pathological conditions like diabetes, hypothyroidism, hypertension, chronic airway obstructive disease were not included.
- Pregnant and lactating women were not included in the study.
- Patients of HIV with pulmonary tuberculosis were not included.

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A total of 120 patients, who fulfilled the inclusion criteria as well as exclusion were included in the study. Study period was between February 2012 to August 2012. Statistical analysis simple percentage and proportion.

Results

A total of 120 patients of pulmonary TB were screened for cutaneous manifestations. Out of these 78 patients were male and 42 were female. Age group varied from 15 years to 70 years. Cutaneous manifestations were observed in 36 patients (30%). Following manifestations were observed (Table I)

Table I: Observed manifestations.

S. no.	Dermatological finding	No. of patients	Percentage (%)
1	Xerosis	16	13.3
2	Pruritus	14	11.6
3	Acneform eruptions	9	7.5
4	Lichenoid eruptions	5	4.16
5	Steven Johnson syndrome	1	0.83
6	Tuberculids	1	0.83
7	Lupus vulgaris	1	0.83
8	Urticaria	1	0.83
9	Herpes Zoster	1	0.83

The youngest patient was a 15-year-old male who showed tuberculids, while the oldest patient was of 62 years who complained of pruritus. In general, xerosis and pruritus were more common in older age group while uncommon manifestations like Steven Johnson syndrome, tuberculids, lupus vulgaris were found in younger patients. Age distribution of skin manifestations is shown in table II.

Xerosis and pruritus were most commonly seen in 16 (13.3%) and 14 (11.6%) patients respectively. Less common were acneform eruptions and lichenoid eruptions, which were observed in 9 and 5 patients respectively.

Table II: Age distribution of cutaneous manifestations.

S. no.	Age group (years)	Male	Female	Total
1	15 - 25	3	2	5
2	26 - 35	5	2	7
3	36 - 45	6	5	11
4	46 - 55	6	3	9
5	56 - 65	3	1	4
		23	13	36

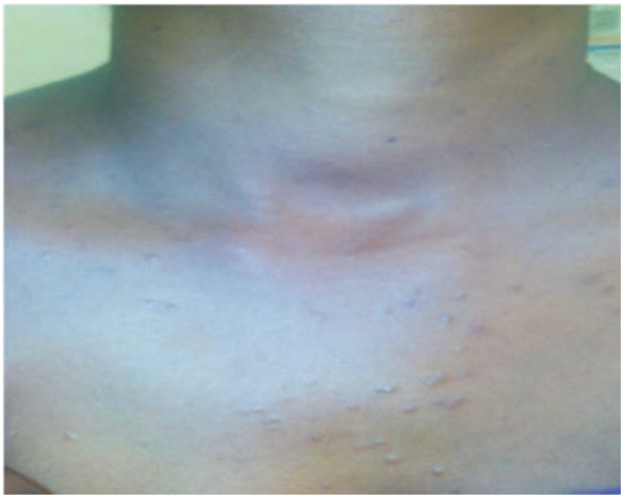

***Fig. 1**: Acneform eruptions due to isoniazid.*

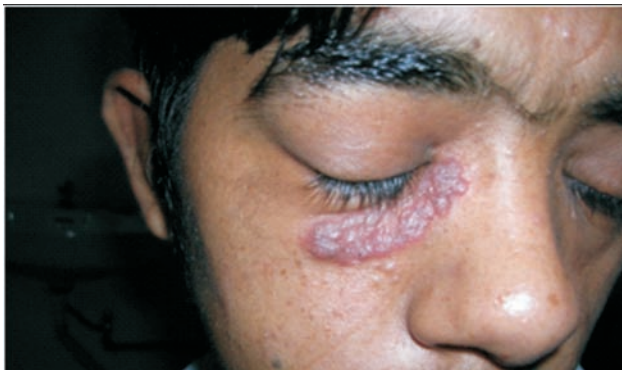

***Fig. 2**: Lupus vulgaris of face in a patient of pulmonary TB.*

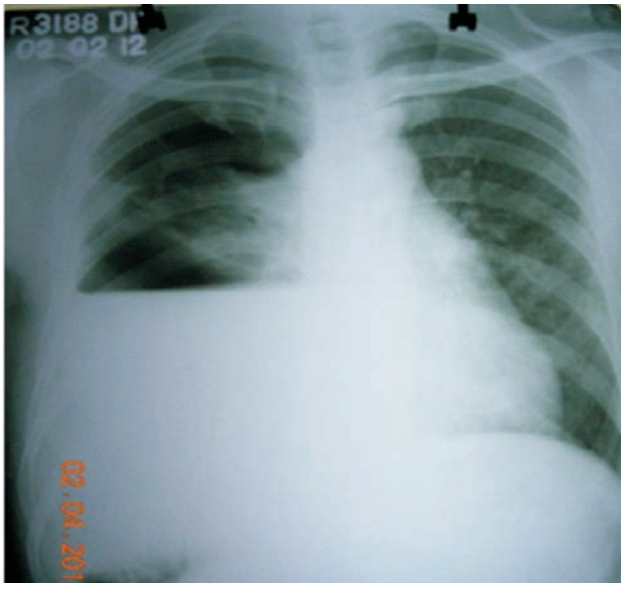

***Fig. 3:** Chest radiograph showing right-sided pyopneumothorax.*

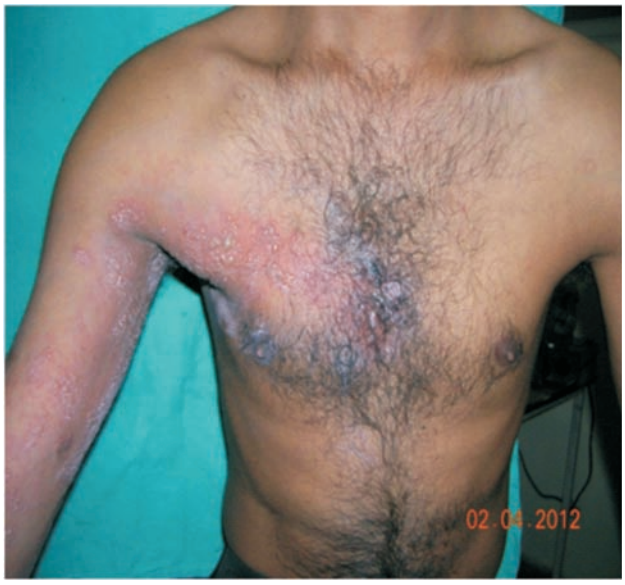

Fig. 4: *Herpes zoster involving the right-sided thoracic dermatome.*

Uncommon manifestations, namely, Steven Johnson syndrome, tuberculids, lupus vulgaris, and urticaria were found in one patient each.

One interesting observation of herpes zoster was found in an otherwise immunocompetent 30-year-old patient. There was right-sided tuberculous pyopneumothorax and herpes zoster involving the right thoracic dermatome. It may be a chance observation, as herpes zoster is not very common in the young age group.

Discussion

Cutaneous manifestations due to anti- tuberculous drugs have been reported in various previous studies[4,5,6,7,8]. Most common manifestations observed have been pruritus and xerosis only. We also observed the same in our study. Patel and Marfatia reported pruritus and acneform eruptions in their study with respective incidence of 1% and 0.43%[6]. Sharma and Kothari reported 1.43% incidence of acneform eruptions due to anti-tuberculous medicines in their study while we have found higher incidence, i.e., 7.5%[5]. Variation in our study may be due to the much smaller sample size of the study.

It has to be understood whether it was a coincidence or any causal relationship. Cutaneous and neurological complications of HZ are well known and documented in literature. Tribble *et al* have reported cases of colonic pseudo-obstruction as a result of dermatomal zoster[9]. Lung involvement with corresponding herpes zoster in a patient has been suggested by Andrews *et al*[10,11]. As generally agreed theory, herpes zoster results from reactivation of dormant varicella zoster in the dorsal root ganglion. Immunocompromised states also predispose to more visceral complications of HZ. The virus is neurotropic and on activation lead to lesions in the skin supplied by that particular nerve.

Conclusion

Skin being the largest organ of body is frequently affected in patients of pulmonary tuberculosis, either directly due to disease or because of side-effects of anti-tuberculous drugs. At times it becomes challenging to correlate the skin finding to the primary cause. Hence it requires a special interest of the treating physician and dermatologist to diagnose and treat the same.

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"I shall not waste my days in trying to prolong them."

– Ian L. Fleming.

CASE REPORT

JIACM 2013; 14(3-4): 287-8

Oesophagopleural fistula secondary to empyema thoracis

I Masood, V Dutta**, S Singh**, S Chand***, S Sune****, M Rakesh******

Abstract

A young female with Staph. pneumonia complicated by bilateral empyema thoracis who developed oesophagopleural fistula in an ICU setting and finally succumbed to her disease is presented here.

Key words: Oesophagopleural fistula, empyema, intercostal tube drain (ICTD).

Introduction

Oesophagopleural fistula is a communication between oesophagus and pleural space and is uncommonly found in clinical practice. Common causes are oesophageal disease, trauma, or during thoracic surgical procedures[1]. Rarely, it may occur due to chronic empyema thoracis not related to major thoracic surgery[2]. A young female with non-tuberculous bilateral empyema which was complicated by oesophagopleural fistula is reported here.

Case report

A 38-year-old immunocompetent female was admitted to the emergency room with complaints of high grade fever with chills and productive cough with acute onset breathlessness of 1 day duration. On examination, her pulse rate was 130/m, BP – 106/70 mm Hg, RR – 30/min, Temp – 102° F, SpO_2 – 98%, and mild pallor was present.

Chest examination showed diminished breath sounds at lung bases on both sides,with crackles in infraaxillary area. On ABG, PH was 7.41, pO_2 - 66.4, pCO_2 - 23.3, HCO_3 - 14.5, Na $\pm$ 128 K $\pm$ 3.3. Diagnostic pleural tap showed WBC – 1,200/mm^3 with predominant polymorphs, and pleural fluid culture grew *Staph. aureus*. CVS and per abdomen examination was normal. The patient was managed with IV antibiotics, bilateral ICTD and other supportive therapy in an ICU setting. Due to continued respiratory distress, the patient was put on elective mechanical ventilation. Bedside fibreoptic bronchoscopy showed no breach in the bronchial lining, no communication between trachea and oesophagus, and no endobronchial lesion causing oeshophagopleural communication was found. Bronchial aspirate was negative for Z-N stain and Gram's stain. Patient became symptomatically better, there was minimal IC tube drainage and the intercostal tube was removed on the 7th day; and the patient was extubated on the 8th day.

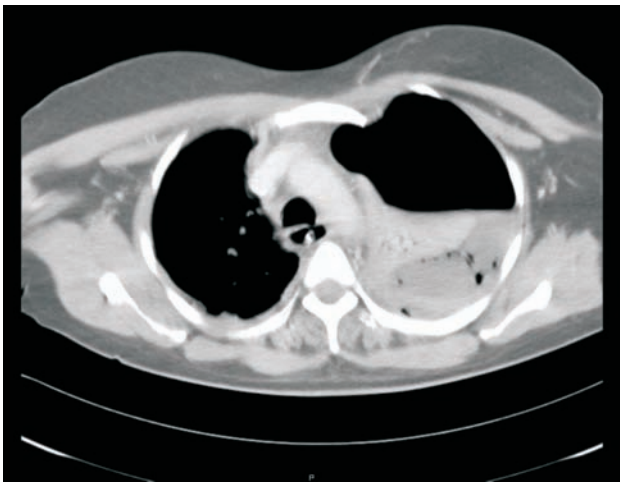

***Fig. 1**: CECT of thorax showing empyema bilaterally (left > right).*

However, she failed to maintain saturation and was re-intubated the next day. Tracheostomy was done in view of long-term ventilator requirement. CECT thorax (Fig. 1) showed re-accumulation of empyema bilaterally (lt > rt). ICTD was re-inserted with streptokinase instillation. Repeat pleural fluid culture grew *Klebsiella pneumoniae* and antibiotics were modified to imipenem/teicoplanin/amikacin and parenteral metronidazole. Repeat CT thorax showed oesophagopleural fistula. Endoscopy showed lower oesophageal transmural tear with oesophagopleural fistula. Dye instillation was avoided because fistula was confirmed on endoscopy. Oesophageal stent was placed and feeding gastrostomy done, but patient continued to worsen and finally expired.

Discussion

Oesophagopleural fistula commonly occurs following rupture of oesophagus subsequent to oesophageal disease, trauma, oesophagoscopy, or after various

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thoracic surgical procedures like pulmonary resection, hiatus hernia repair, or resection of thoracic aortic aneurysm, etc. Rarely, it may occur due to chronic empyema thoracis – tuberculous and non-tuberculous . Only a few case reports regarding this condition are available in literature. In an exclusive review of 101 cases of oesophagopleural fistulae, Tokaro *et al* found chronic empyema without major thoracic surgical intervention to be the only cause in 35 cases[3]. Adeyama *et al* have reported one such case of tuberculous empyema complicated by oesophagopleural fistula[4]. The present case developed this complication due to *Staphylococcus aureus* pneumonia leading to bilateral empyema causing oesophagopleural fistula. Singla reported a similar case due to pseudomonal infection[5].

Usually it takes a long time for oesophagopleural fistula to develop after empyema. The present case developed this complication following staph. empyema within a short duration of one month, which is an unusual feature. Generally, most oesophagopleural fistulae are located in mid-thoracic region near the bifurcation of trachea. The true pathogenesis of many chronic oesophagopleural fistulas remain obscure, but chronic empyema of long duration with or without thoracic surgery is responsible for most cases. Other causes are rupture of suppurating or caseating lymph nodes which have previously established connection with oesophagus into pleural or extrapleural space, or rupture of traction diverticulum of oesophagus. Oesophageal rupture by a hard intercostal drainage tube has also been reported.

Treatment of oesophagopleural fistula can be done by surgery or by conservative approach. Conservative treatment includes control of infection with proper antibiotics, drainage of pleural pus (empyema) by intercostal tube drainage, adequate nutrition with giving rest to oesophagus by gastrostomy or jejunostomy. Conservative methods are preferred in debilitated high-risk patients who cannot withstand major surgery, but carry a > 90 per cent mortality rate. Surgical treatment includes direct closure of fistula, resection, and re-anastomosis of oesophagus, Schede thoracoplasty, etc.

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2. Raj B, Talwar MM. Pleuroesophageal fistula as a complication of empyema thoracis. *Indian J Chest Dis & All Sci* 1984; 24: 294.
3. Tokaro T, Walkup HE, Okano T, Oteen NC. Oesophagopleural fistula as a complication of thoracic surgery: A collective review. *J thoracic Cardiovasc Surg* 1960; 40: 179.
4. Adeyama AO, Omole CO. Oesophagopleural fistula complicating a case of Tuberculous pyopneumothorax. *Tubercle* 1984; 365: 59.
5. Singla R, Bhagi RP, Pritam *S et al*. Oesophago pleural fistula secondary to empyema thoracis 1JCD 1988; 30: 225-229.
6. Johnson AO, Grillo IA, Adebonojo SAA. Oesophagopleural fistula. A complication of chest intubation for empyema. *JNAT Med Assoc* 1980; 72; 315.

Indian Association of Clinical Medicine

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IACMCON-2013

21st Annual Conference of Indian Association of Clinical Medicine

26th - 27th October, 2013 • Kota, Rajasthan

SCIENTIFIC PROGRAMME

Day 1 – Saturday, 26th October, 2013 • Auditorium, Medical College, Kota

08.30 am	–	Registration	
Infections			
09.00 am	–	Nosocomial Infections: Tough Challenge for Clinicians	NK Soni
09.30 am	–	Sepsis – What is New?	MPS Chawla
Oncology			
10.00 am	–	CML: Approach to Treatment	Vineet Talwar
10.30 am	–	Multiple Myeloma – How it presents to an Acute Care Physician	Madhuchanda Kar
Diabetes			
11.00 am	–	Early Insulin Therapy at Onset of Diabetes	Ajay Kumar
11.30 am	–	DPP-4 Inhibitors	Ambrish Mittal
12.00 pm	–	Diabetic Ketoacidosis	Shashank Joshi
Prof. MC Gupta Oration			
12.30 pm	–	100 years of the Journey of Insulin and Future Directions	YP Munjal
01.00 pm - 01.30 pm	–	Inaugural Ceremony	
01.30 pm - 02.15 pm	–	Lunch	
Guest Lecture			
02.15 pm	–	Science of Man	BM Hegde
Nephrology			
02.45 pm	–	Acute Kidney Injury in the ICU setting	PP Verma
Clinical Medicine Update			
03.15 pm - 4.15 pm	–	Thyrotoxicosis – Clinical Profile and Management	AK Gupta
03.45 pm	–	Approach to Unknown Poisoning	Vikas Loomba
Dr. GS Sainani & Dr. (Mrs.) Pushpa G Sainani Oration			
04.15 pm	–	Cancer Screening – A Physician's Perspective	GL Awasthi

Rheumatology

04.45 pm	–	Axial Spondyloarthropathy	Uma Kumar
05.15 pm	–	Mimickers of Rheumatoid Arthritis	Harpreet Singh
06.30 pm	–	Convocation	
08.00 pm	–	General Body Meeting	
08.30 pm	–	Gala Dinner	

Day 2 – Sunday, 27th October, 2013 • Auditorium, Medical College, Kota

Gastroenterology

08.30 am	–	Acute abdomen – Non-surgical causes	Sumeet Singla
09.00 am	–	Fatty Liver – Can we ignore it any longer	Rajesh Upadhyay

Haematology

09.30 am	–	Challenges in Management of Aplastic Anaemia	Manoranjan Mahapatra
10.00 am	–	Recent Advances in Anti-Coagulation Therapy	JS Gujral

Presidential Oration

10.30 pm	–	Current Scenario and Future of Geriatric Care in India	Gursharan Siddhu

Prof. BC Bansal & Mrs. Uma Bansal Oration - 2013

11.00 am	–	Genetic Basis of Diabetic and Non-Diabetic Renal Disease	OP Kalra

Cardiology

11.30 am	–	Non-ST elevation MI	RR Mantri
12.00 noon	–	CT Coronary Angio – An Internist's perspective	Harsh Mahajan
12.30 pm	–	Non-Coronary Cardiac Complications of Diabetes	Murlidhar Rao

Clinico-Pathological Conference (CPC)

01.00 - 02.00 pm	–	CPC
02.00 - 02.45 pm	–	Lunch

Dr. GB Jain Oration

02.45 pm	–	Hypertension – History and Advances	AK Gadpyle

General Medicine

03.15 pm	–	Relevance of Latent TB Infection Treatment in TB High-burden Countries	SK Sharma
03.45 pm	–	Epilepsy: Clinical Perspectives and Management	Manjari Tripathi
04.15 pm	–	Enteric Fever	Alladi Mohan
04.45 pm	–	Management of Difficult Asthma	Randeep Guleria

HIV Medicine

05.15 pm	–	Fungal infections in HIV: A Case-based Presentation	Dipanjan Bandyopadhyay
05.45 pm	–	ART Guidelines	BB Rewari

Scientific Committee

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26th-27th October 2013

Auditorium, Medical College, Kota

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