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VIEWPOINT

JIACM 2013; 14(2): 106

Biomimicry: The science of learning from nature

*BM Hegde**

"When one tugs at a single thing in nature, we find it attached to the rest of the world."

– John Muir.

I keep reminding the readers about our wrong efforts at learning science by teaching nature a lesson or two. That we could have a better science by understanding nature's working better, has been my hypothesis. I was introduced to some work being done at the Karolinska Institute in this direction by an old student of mine, Dr. Sunder. He wrote to tell me that my pet theory of learning from nature has now been taken up in the West and they also think it might yield better results. We shall discuss just one area for this write-up.

Chronic kidney failure (CKF) has been a very lucrative medical business for the corporate lobby next only to cardiac interventions and keeping dying patients in the ICU for the last ten days. In the US there are many "dialysis only" facilities. They are like the hair cutting shops. Patients walk in and remain there for a few hours and get dialysed and go home to come back again at periodic intervals. They might have about a dozen beds at a given time used for dialysis. Reports say that this is such a good business that these doctors do not advice their patients kidney transplant at the right time when it could be more beneficial to the patients. Instead they wait till the last minute when transplant could be more dangerous and less useful. All this is because they want their clients for longer time to make more money. This is the audit report. Kidney transplant is another big business which all of us know in great detail.

But look at nature. The American native black bear (Ursidae) is a good example here. These bears hibernate for 3 - 5 months without any food or water. They do not make any urine and have no exercise at all, they remain immobile for months. They sleep all the time. But when they wake up they are as fit as they were and might even attack their enemy with the same ferocity as they could do while they were ambulant. It is interesting to note that when they wake up they have very low urea nitrogen levels, healthy lean body mass, very strong bones, and no evidence of any thrombotic complications! If only our scientists could find out how and why these bears do not develop uraemia, muscle wasting, bone density loss (osteoporosis) and atherosclerosis and thrombotic complications we will have found out novel and easy methods of treating chronic kidney failure patients without dialysis and transplant as of now!

The million dollar question here is: who will fund this "rice bowl breaking" research effort? If successful, this will demolish the very lucrative dialysis and kidney transplant businesses. Please understand that neither dialysis nor kidney transplant is a cure for chronic kidney failure. They are only quick-fix solutions of modern medical science, like many others like them. But the industry likes these quick fixes in place of permanent cures!

Contrast this with our science where we create disease models in animals, mostly rats, dogs, and pigs. We try and study them to gain our present wisdom. What we do not realise is that they are in no way closer to human physiology and when we create human diseases in them they react, sometimes in a diametrically opposite direction. One example would do to explain. We produce heart failure in rats and then use our new chemical molecules on them to see if they work and if they do, we use them in humans. Some years ago there was a wonder drug called, milrinone, a cousin of amrinone. This showed wonderful results in rats in the treatment of heart failure, one of the biggest problems of old age. The company was so impressed that they convinced (lobbied) the FDA to pass it even without human studies. Indian "great" cardiologists used to get the drug from USA for their rich patients, quite a lot of whom met their makers prematurely, but the death was blamed on the bad heart failure. Soon enough the first human study PROMISE (prospective randomised milrinone evaluation study) was started. Within six months into the study, the preliminary report showed 37% extra unexplained deaths in the milrinone wing of the trial compared to the placebo, and therefore the study was stopped and the drug withdrawn from the market. Lots of people had died by then. Later physiologic studies showed that the drug, in fact, helps a rat's heart while it is dangerous for the failing human heart! We do not go into the details here.

Respect nature as your mother and learn from her; if you abuse nature she will kick you in the teeth! Scientists! Are you listening? Long live mankind learning from nature as our Indian scientists of yore did.

"In all things in nature there is something of the marvellous."

– Aristotle.

**** Padma Bhushan; Former Vice-Chancellor, Manipal University; Editor-in-Chief, The Journal of the Science of Healing Outcomes; Chairman, State Health Society's Expert Committee, Govt. of Bihar, Patna; Visiting Professor of Cardiology, The Middlesex Hospital Medical School, University of London, U.K.; Affiliate Professor of Human Health, Northern Colorado University, U.S.A.***

ORIGINAL ARTICLE

JIACM 2013; 14(2): 107-10

Role of microalbuminuria before and after chemotherapy in non-Hodgkin's lymphoma

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Abstract

Objectives: *To evaluate the role of microalbuminuria in patients of non-Hodgkin's lymphoma (NHL) before and after chemotherapy.*

Study design: *The study was conducted in 30 newly diagnosed patients of NHL. The median urinary albumin excretion (UAE) levels before and after treatment were measured. Microalbuminuria was defined as albumin excretion > 20 µg/min. Patients were categorised according to Ann Arbor staging and international prognostic index (IPI). Patients with stage III - IV (Ann Arbor staging) were found to have increased albumin excretion than patients with stage I-II. The median urinary albumin excretion levels before and after treatment were 24.65 µg/min and 13.05 µg/min respectively (p= 0.001). Response to treatment was categorised as complete remission or complete remission unconfirmed/uncertain (CR or CRu), partial remission (PR), stable disease (SD), or progressive disease (PD). 13 patients not having microalbuminuria at diagnosis responded to treatment, whereas out of 17 patients having microalbuminuria, 11 had PR, 4 had SD and 2 progressed with the disease (PD). Furthermore, patients achieving CR/CRu or PR had significant fall in post-treatment UAE levels than pre-treatment levels, whereas post-treatment increase in UAE levels occurred in patients with SD or PD.*

Conclusion: *Urinary albumin excretion represents the tumour load, progression of the disease, and also account for predictability of response to treatment. UAE, thus can be used as a non-invasive tool for assessing tumour burden and also for prediction of response to treatment.*

Key words: *Non-Hodgkin's lymphoma (NHL), urinary albumin excretion (UAE), tumour load, response to treatment.*

Introduction

Microalbuminuria is defined as slightly elevated levels of urinary albumin excretion below detection limit of urinary dipstick test[1]. Microalbuminuria, though considered a non-specific marker of both systemic and local inflammation[2,3], over a period of time has emerged as a useful predictor of outcome in several clinical situations[4-7].

The pathogenesis of microalbuminuria is assumed to be due to cytokines mediated inflammatory reactions, leading to increased glomerular permeability[8,9]. Various studies have shown the presence of microalbuminuria in inflammatory and malignant disease[10-12]. The variations in urinary albumin excretion (UAE) levels have been well-demonstrated in cancer patients with the increased tumour load associated with increased UAE[10,11,13]. Further institution of antineoplastic agents resulted in reduction of UAE[10,11,14], thus signifying its clinical and prognostic implications.

Microalbuminuria has been reported as a surrogate marker of disease in various reports. However, its presence as a predictor of clinical response has not been studied in detail so far. The clinical implications would increase considerably if UAE is shown to be a predictor of treatment response and disease progression. Thus, in order to explore the clinical and prognostic implications of UAE, we planned the study in patients of non-Hodgkin's lymphoma (NHL).

Material and methods

Study design

30 newly diagnosed, biopsy-confirmed patients of NHL attending the haematology clinic at PGIMS, Rohtak, Haryana, were enrolled for the study. The histopathological diagnosis was made according to the updated WHO classification[15]. The clinical staging was done using Ann Arbor staging system and international prognostic index (IPI) was determined in all patients. CT scan of thorax, abdomen, bone marrow aspiration/ biopsy was done to confirm the clinical staging. In order to avoid confounding factors that might influence the UAE (i.e., patients with history of coronary artery disease, diabetes mellitus, hypertension, acute infections, pancreatitis, chronic kidney disease, congestive heart failure, rheumatoid arthritis, adult respiratory distress syndrome) were excluded from the study. All patients gave written consent and the institutional review board at the PGIMS approved the study protocol.

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Treatment

All the patients were treated with standard chemotherapy for NHL (CVP for low-grade indolent lymphoma and CHOP for high-grade aggressive lymphoma). According to standard guidelines, response to treatment was categorised as complete remission, or complete remission unconfirmed/uncertain (CR or CRu), partial remission (PR), stable disease (SD), or progressive disease (PD)[16, 17].

Urine albumin excretion

Microalbuminuria was defined as albumin excretion > 20 µg/min. Every patient was asked to provide 2 urine samples one week apart before the start of chemotherapy. Later on, post-treatment samples (two samples one week apart) were obtained. The samples were taken 2 - 4 weeks after completion of last treatment in order to avoid the possible effect of therapy on renal profile. UAE was determined by nephelometry[18] and the result of UAE was taken as average of sample UAE values.

Statistical analysis

Results are expressed as median values and ranges because of skewed distribution. The average UAE of two urine samples collected (pre- and post-treatment) was calculated. Continuous variables were compared using the Mann–Whitney U test and Wilcoxon signed rank test. Differences between categorical variables were analysed by Fisher exact test. A p value of < 0.05 was taken as significant.

Results

Patient profile and staging of disease

The study was carried out in 30 newly diagnosed, biopsy-proven NHL patients. The median age of patients was 53 years (range 16 - 80). Male to female ratio was 3:2. According to Ann Arbor staging, 19 patients were in advanced stages (III - IV) and 11 were in early stages (I - II) at diagnosis. The Karnofsky performance status of ≤ 70 was present in 16 patients as compared to 14 patients who had ≥ 70. The IPI (international prognostic index) score of ≥ 2 was considered to be a poor prognostic marker and was present in 20 patients.

Urine albumin excretion and disease severity

The median pre-treatment UAE in stage I - II was 14.2 µg/min as compared to 32.5 µg/min in stage III - IV, and the difference was statistically significant ($p = 0.01$). Similarly, the patient having IPI ≥ 2 had a higher median pre-treatment UAE than the patients with IPI < 2 (32.15 µg/min vs. 14.0 µg/min), and the difference was statistically significant ($p = 0.01$) as depicted in Table I.

Table I: Urine albumin excretion and disease severity.

Ann arbor staging	I - II	14.2 µg/min*	p = 0.01
	III - IV	32.5 µg/min	
IPI	≥ 2	32.15 µg/min	p = 0.01
	< 2	14 µg/min	

** mean urinary albumin excretion (UAE)*

Treatment

Out of 30 patients, 19 patients were given CHOP therapy and 9 patients were treated with CVP. The remaining 2 patients were treated with combined modality (radiotherapy and chemotherapy both) as shown in Table II.

Table II: Treatment in 30 patients of NHL.

Therapy	No. of patients
CHOP	19
CVP	9
Radiotherapy and chemotherapy both	2

Treatment response and microalbuminuria

17 patients were having microalbuminuria at the time of diagnosis, whereas there was no microalbuminuria in 13 patients. All 13 patients not having any microalbuminuria responded to treatment, whereas out of 17 patients having microalbuminuria, 11 patients responded to treatment. 13 patients achieved complete response (CR/CRu), 11 had partial response (PR), whereas the disease was stable (SD) in 4 patients and progressive (PD) in 2 patients as shown in Table III.

Table III : Response to treatment in patients.

Response	No. of patients
CR/CRu	13
PR	11
SD	4
PD	2

Table IV: UAE levels in patients before and after treatment.

	UAE	
Before treatment	24.65 µg/min	p = 0.001
After treatment	13.05 µg/min	

Pre- and post-treatment UAE

The median urinary albumin excretion was 24.65 µg/min before treatment whereas the median post-treatment UAE was found to be 13.05 µg/min. The reduction in UAE was statistically significant ($p = 0.001$) as shown in Table IV.

Furthermore, the patients who achieved CR, the median UAE was 10.9 µg/min as compared to 19.19 µg/min in the pre-treatment period (p = 0.0002). Similarly, the difference in UAE levels was significant in patients achieving PR (13.2 µg/min vs. 19.6 µg/min; p = 0.0001). In contrast, the patients with no response to treatment (SD + PD) had higher post-treatment urine albumin levels than pre-treatment levels (66.35 µg/min vs. 59.45 µg/min). The results are shown in Fig. 1.

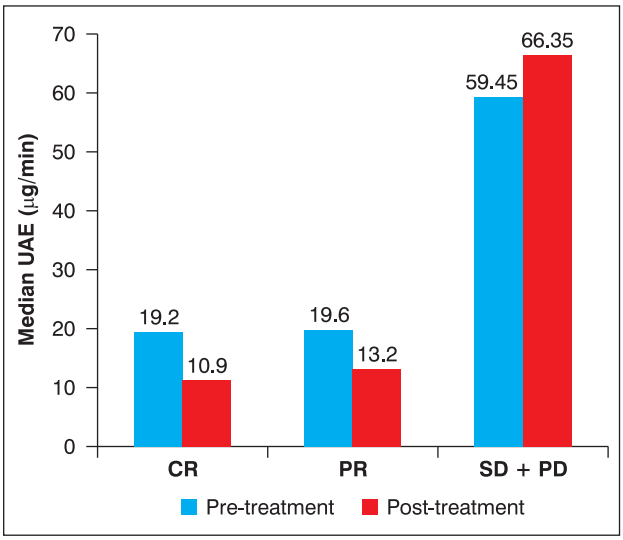

Fig. 1: *Medium UAE and patients having CR, PR and SD + PD.*

Discussion

Microalbuminuria represents a state of inflammation, both systemic and local[2,3]. Various reports have shown it to be a marker of malignancy with increased levels associated with increased tumour load, but the studies regarding its prognostic implication and clinical response after treatment in malignancy are scarce. In view of the potential prognostic indicator at diagnosis and post-treatment, the present study was planned in NHL patients to find out alterations, if any, in UAE levels with clinical stage of disease and before and after therapeutic intervention. The study enrolled 30 patients and the conditions that might influence the UAE levels as described earlier, were excluded. We came out with some interesting observations which are discussed here.

We found a positive correlation between UAE levels and the tumour load, with the patients having class III - IV grade lymphoma (Ann Arbor stage) higher median level of UAE than the patient in class I - II lymphoma (32.5 µg/min vs. 14.2 µg/min). Similarly, the median UAE level was more in patients having IPI $\geq$ 2 (median UAE 32.15 µg/ min) than patients having IPI < 2 (14.0 µg/min) and the difference was statistically significant. These findings imply that the more UAE levels were associated with advanced disease.

The pre-treatment and post-treatment median levels of UAE level were 24.65 µg/min and 13.05 µg/min respectively. The difference was significant, implying that the treatment accounted for a decrease in UAE levels. The decrease in UAE level with treatment, thus, validated the previous findings that variation in UAE levels parallels with the tumour burden[2,9,10].

At diagnosis, 13 patients had no microalbuminuria and 17 patients had microalbuminuria. After treatment, all the 13 patients responded to treatment (CR + PR) whereas 11 out of 17 patients achieved response (CR + PR) and no response was seen in 6 patients (SD + PD). These findings represent that the patients having no microalbuminuria at diagnosis responded much better to treatment than the patients having microalbuminuria at diagnosis. On further elaboration of data, a statistical significance was there in patients with response (CP + PR) having median pre-treatment UAE level 21.1 µg/min as compared to median post-treatment UAE level 11.2 µg/min (p = 0.0002). On the other side, median post-treatment UAE level rose to 66.35 µg/min as compared to 59.45 µg/min in the pre-treatment phase in nonresponders (SD + PD). These findings suggest that nonresponders worsened with the disease as compared to responders (indicated by increased post-treatment UAE levels).

Our study, thus, suggests the possible presence of microalbuminuria in a vast majority of patients having NHL, its positive correlation with the tumour load, and its prognostic indication in NHL. The increase in UAE level with tumour burden, in nonresponders, and decrease in responders favours the association between NHL and UAE. The findings are in accordance with the other studies[2,7,9].

The exact mechanism behind our findings is not well known, but in the absence of other confounding factors which might influence the albumin excretion, we hypothesised that malignancy, being a state of chronic inflammation, might cause an increase in pro-inflammatory cytokines, thus leading to renal excretion of albumin. The pro-inflammatory cytokines have been shown to lead to cascade resulting in increased glomerular permeability and thus albumin excretion[9].

Conclusion

Our data demonstrates the frequent presence of microalbuminuria in NHL patients (57% of cases). The level of UAE parallels with the tumour load, and the level may be considered as a predictor of treatment response. It is thus suggested that the presence of microalbuminuria in NHL and its pre- and post-treatment level might be of help in predicting the response to treatment. Since the sample

size was small, further large scale studies are warranted in this regard to know the exact association between the UAE, the disease severity, and its prognostic implication in response to treatment in NHL.

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ORIGINAL ARTICLE

JIACM 2013; 14(2): 111-4

Peripheral vascular disease – a silent assassin: Its rising trend in Punjab

Ashok Khurana, Preeti Dhoat**, TS Marwaha****

Abstract

Objective: To determine the prevalence of peripheral arterial disease in type 2 diabetes mellitus using the ankle-brachial pressure index and to educate the patients regarding risk factor modification and importance of early intervention to prevent future progression.

Research design and methods: A 12 MHz Doppler probe was used in the arms and legs to assess the ankle brachial index (ABI) in 200 type 2 diabetes mellitus patients aged more than 40 years. A thorough history of patients including age, smoking history, history of symptoms of peripheral arterial disease, complete physical examination, and routine investigations were collected at the time of enrolment for all subjects. A ratio of the highest blood pressure from the posterior tibial or pedal arteries of each leg to the highest blood pressure from the brachial arteries < 0.9 was considered abnormal.

Results: Abnormal ABIs were found in 33% (66/200) patients with type 2 diabetes mellitus. 45.5% patients had ABI 0.80 - 0.89, 33.3% patients had ABI 0.50 - 0.79, and 21.2% patients had ABI < 0.5.

Conclusions: Prevalence of peripheral vascular disease in type 2 diabetes mellitus is on rise in northern India.

Key words: Type 2 diabetes mellitus, peripheral vascular disease.

Introduction

Peripheral vascular disease is a major macrovascular complication of diabetes mellitus[1]. Because of the unique involvement of distal pattern of vessels and invariable association with neuropathy, peripheral arterial disease in diabetics presents late, having already developed limb-threating ischaemia[2]. Ankle-brachial pressure index is a noninvasive testing method which greatly increases the accuracy of clinical diagnosis for the presence of arterial disease and serves as an objective index to follow the natural history of the disease[3]. Ankle-brachial pressure index is the most efficient, objective, and practical means of documenting presence and severity of peripheral arterial disease[4]. In the present study, 200 patients with type 2 diabetes mellitus were enrolled to find out prevalence of peripheral vascular disease using ankle-brachial pressure index. The data thus obtained was analysed statistically.

Material and methods

Study group: 200 patients aged more than 40 years, who were admitted in various units of the Department of Medicine of Sri Guru Ram Das Hospital, Amritsar, Punjab with type 2 diabetes mellitus were enrolled. Patients of type 1 diabetes mellitus, smokers, those having ischaemic heart disease, those with history of hypertension before diagnosis of type 2 diabetes mellitus, and those with previous history of cerebrovascular accident or heart disease were excluded from the study.

Study protocol

The ABI was measured with a blood pressure cuff and a Doppler ultrasound sensor. The cuff was applied to both arms and ankles. The Doppler probe was used to determine systolic blood pressure in both brachial arteries in the antecubital fossa, and in the right and left posterior tibial arteries, and the right and left dorsalis pedis arteries. With an 12 MHz Doppler probe we obtained the systolic arterial pressure when the first Doppler signal was heard. The ABI for each leg was calculated as the ratio of the higher of the two systolic pressures (posterior tibial or dorsalis pedis) in the leg and the higher systolic pressure of either the left or right arm. The method used was in accordance with a recent consensus statement on measuring the ABI. An ABI < 0.9 in either leg was considered abnormal, suggesting peripheral arterial disease; progressively lower ABI values indicate more severe obstruction. A thorough history of patients including age, smoking history, history of symptoms of peripheral arterial disease, complete physical examination and routine investigations including haemoglobin, total leucocyte count, differencial leucocyte count, fasting blood sugar, HbA1C level, blood urea, serum creatinine, sodium, potassium, lipid profile, urine (complete), and ECG were done.

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Statistical analysis

Statistical analysis was with chi-square test and univariate regression analysis.

Results

Abnormal ABIs were found in 33% (66/200) patients with type 2 diabetes mellitus enrolled in the present study. Out of this, 45.5% patients had ABI 0.80 - 0.89, 33.3% patients had ABI 0.50 - 0.79, and 21.2% patients had ABI < 0.5. Among these 66 patients having peripheral vascular disease, females had higher percentage of peripheral arterial disease as compared to males 62.1% vs 37.9% ($p < 0.05$). 13.6% (9) patients belonged to the age group of 40 - 49 years. 34.8% (23) patients belonged to the age group of 50 - 59 years. 51.6% (34) patients belonged to the age group 60 years and above. With increasing age, the prevalence of peripheral arterial disease in type 2 diabetes showed an increasing trend ($p < 0.05$). 39.4% (26) patients were asymptomatic, while 60.6% (40) were symptomatic with symptoms of claudication, rest pain, Leriche syndrome ($p < 0.001$). 18.2% (12) patients had foot ulcer, while 81.8% (54) patients had no such abnormality ($p < 0.001$). 36.4% (24) patients had HbA1C levels > 7, while 63.6% (42) had HbA1C levels < 7. Overall, patients with

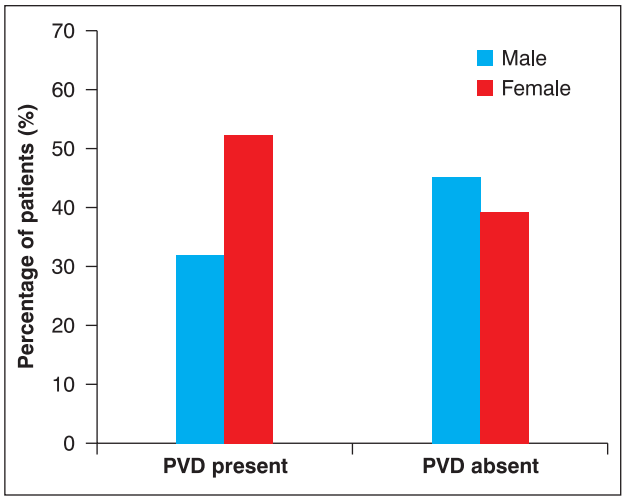

Fig. 1: *Gender-specific prevalence of peripheral vascular disease.*

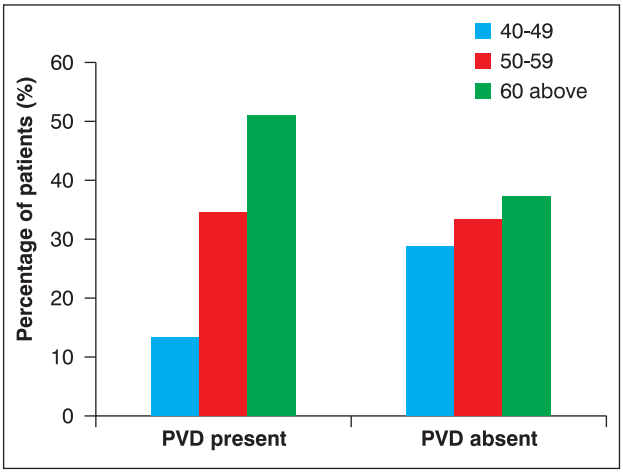

Fig. 2: *Age-wise distribution of peripheral vascular disease.*

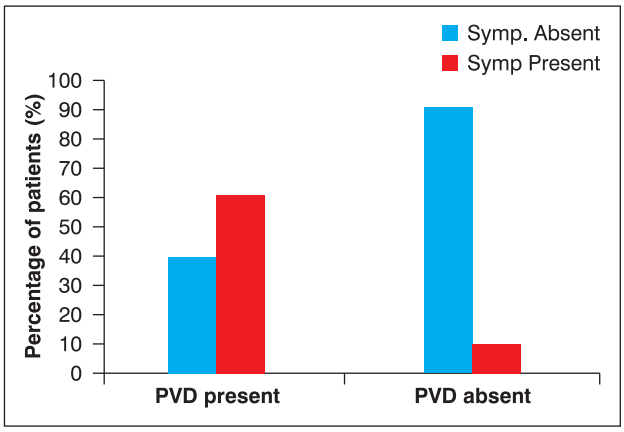

Fig. 3: *Correlation of peripheral vascular disease with clinical approach.*

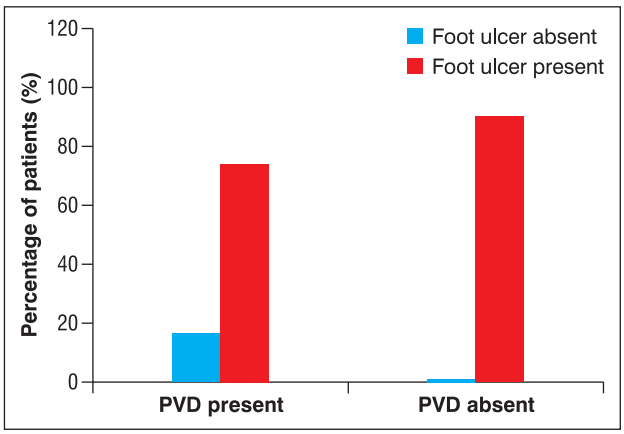

Fig. 4: *Correlation of peripheral vascular disease with foot ulcer.*

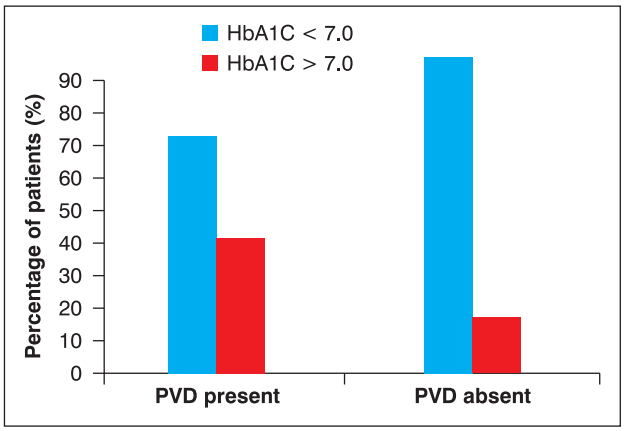

Fig. 5: *Correlation of peripheral vascular disease with HbA1c levels.*

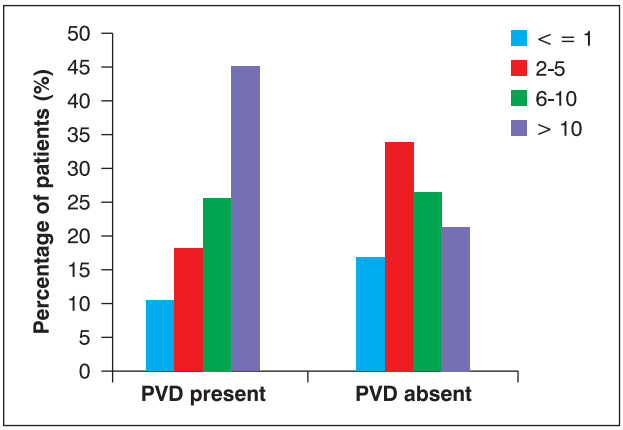

Fig. 6: *Correlation of peripheral vascular disease with duration of diabetes in years.*

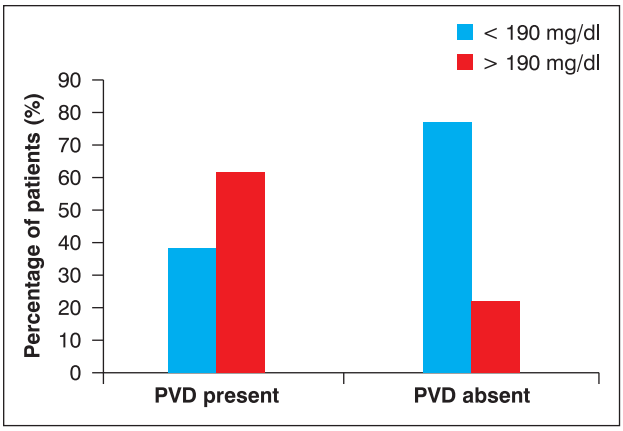

Fig. 7: *Correlation of peripheral vascular disease with LDL Cholestrol levels.*

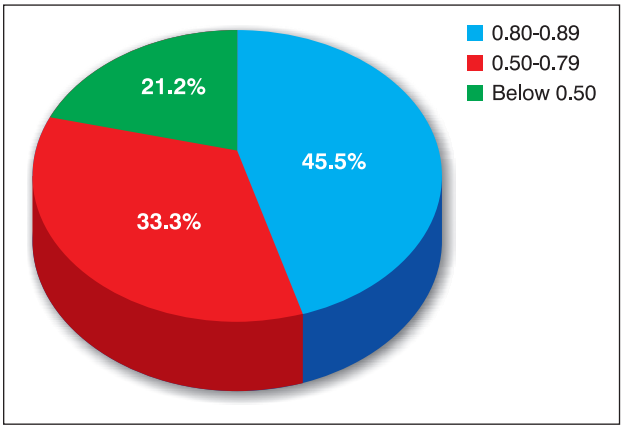

Fig. 8: *Ankle-branchial index stratification in patients having peripheral vascular disease with foot ulcer.*

peripheral arterial disease had correlation with HbA1C levels as compared to patients without peripheral arterial disease ($p < 0.05$). 10.6% (7) patients had duration of diabetes less or equivalent to one year. 18.2% (12) patients had duration of diabetes between 2 to 5 years. 25.8% (17) patients had duration of diabetes between 6 to 10 years while 45.4% (30) patients had duration of diabetes >10 years ($p < 0.001$). 62.1% (41) patients had serum LDL cholesterol levels >190 mg/dl. Out of 134 patients of type 2 diabetes who had no evidence of peripheral arterial disease, 22.4% (30) patients had serum cholesterol levels > 190 mg/dl ($p < 0.001$).

Discussion

Correlation of peripheral vascular disease with gender distribution, age distribution, clinical symptoms, glycosylated haemoglobin, duration of diabetes, LDL cholesterol levels was done. This study showed that females had higher prevalence of peripheral arterial disease as compared to males. While assessing prevalence and risk factors for peripheral arterial disease in an Asian population with diabetes mellitus, Tavintharan *et al* found that prevalence of PAD was more in the female gender[5]. This study showed that with increasing age the prevalence of peripheral arterial disease in type 2 diabetes increased. Lekshmi *et al* while studying the peripheral arterial disease in community-based patients with diabetes in Singapore reported that, prevalence of peripheral arterial disease was positively associated with increasing age[6]. This study showed that high prevalence of symptoms pertaining to lower limbs was found in patients with peripheral arterial disease. This is in concordance with the study done by Buitrón *et al* which showed that the presence of either signs or symptoms was more frequent in subjects with peripheral arterial disease[7]. This study showed that all patients with peripheral arterial disease had higher levels of HbA1C as compared to patients without peripheral arterial disease. Adler *et at* studied potential risk factors for the development of peripheral arterial disease and reported that hyperglycaemia was associated with an increased risk for peripheral arterial disease, independent of other risk factors[8]. Our study also showed positive correlation of duration of diabetes with peripheral vessel disease. Papanas *et al* proved in their study that peripheral arterial occlusive disease in patients was associated with duration of diabetes mellitus[9]. This study also found that peripheral arterial disease was positively correlated with LDL cholesterol levels. This is in concordance with the study done by Cacoub *et al* which showed that LDL cholesterol levels and peripheral arterial disease are positively correlated[10]. The prevalence of peripheral arterial disease using ankle-brachial pressure index in this study was 66 (out of 200 patients), that is 33%. Hirsch *et al* conducted a multicentre, cross-sectional study and detected a prevalence of 29%[11]. Mourad *et al* in a prospective, observational, real-life, epidemiologic study (ELLIPSE) calculated the prevalence of peripheral arterial disease to be 41.1%[12].

Conclusion

The prevalence of peripheral vascular disease in type 2 diabetes mellitus as measured by ankle-brachial pressure index was 33% (66 out of total 200 patients). Hence this increasing trend of peripheral vascular disease requires patient education for risk factor modification and early intervention to prevent future progression.

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ORIGINAL ARTICLE

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Serum testosterone levels in type 2 diabetes mellitus

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Abstract

Background: Type 2 diabetes mellitus has been suggested as one of several chronic conditions in which there is a high prevalence of low testosterone levels. Establishing this relationship conclusively may have profound effects in the management of diabetes and hypogonadism. These results need to be confirmed in more diabetic men, and, therefore an elaborative study was done to confirm these findings in the Indian population.

Objective: This study was performed to evaluate serum testosterone levels in male patients of type 2 diabetes mellitus and their age and BMI-matched controls and find out the correlation between type 2 diabetes and serum testosterone levels

Methods: In this cross-sectional study, carried out in GSVM Medical College, Kanpur, Uttar Pradesh, 50 male patients of type 2 diabetes mellitus and their 50 age and BMI-matched male controls were studied and their serum free testosterone concentrations were measured. Mean age of controls was 52.4 ± 4.2 years and that of diabetic cases was 53.5 ± 4.38. The mean BMI of controls was 23.5 ± 1.9 kg/m² while in cases it was 27.2 ± 2.3 kg/m².

Results: The free testosterone concentrations in diabetic cases was 3.34 ± 0.319 ng/dl which was significantly lower than the free testosterone concentrations in controls (mean value 10.64 ± 0.43 ng/dl) age and BMI groups (P < 0.001). 46 (92%) of 50 cases had subnormal free testosterone concentrations (< 6.5 ng/ dl) while only 4 (8%) of controls had low subnormal serum testosterones (P < 0.001).

Conclusions: Serum free testosterone levels are significantly lower in type 2 diabetics irrespective of age and BMI of patients.

Introduction

Diabetes mellitus is a multifactorial disease which is characterised by hyperglycaemia, dyslipidaemia, involves various organ systems, and results in various long-term complications. Several studies have suggested that men with low testosterone levels are at a greater risk of developing type 2 diabetes mellitus, and that low testosterone levels may even predict the onset of diabetes[1,2,3]

These results need to be confirmed in more diabetic men, and studies need to be done to evaluate whether decreased serum testosterone levels in diabetes are related to age or obesity or is influenced by other variables. Also, since most of the studies done before are on the western population, an elaborative study is required to confirm these findings in the Indian population.

Materials and methods

The study was conducted in GSVM Medical College, Kanpur, UP, India, during the period December 2008 to September 2010. This was a cross-sectional analysis of free testosterone concentrations in 50 type 2 diabetic (mean age 53.5 ± 4.38 years) male patients aged between 21 and 70 years. 50 age and BMI matched non-diabetic controls were also taken for valid comparison. Patients with a known history of hypogonadism, panhypopituitarism, patients not willing for study, patients taking exogenous testosterone, patients with hyperthyroidism, or chronic debilitating disease, such as renal failure, cirrhosis, or HIV, were excluded from the study. The mean level of serum testosterone was calculated in various age and BMI groups and compared with controls.

Free testosterone was calculated from SHBG and total testosterone levels (measured by solid-phase radioimmunoassay) using the method of Vermeulen and colleagues[4]. Hypogonadism was defined as low free testosterone and 6.5 ng/dl was taken as lower limit of normal for free testosterone[5].

Results

Table I shows the baseline demographic characteristics of controls and diabetic cases. Both controls and cases were well-matched with respect to age (53.5 ± 4.38 vs 52.4 ± 4.2 years) and BMI (23.5 ± 1.9 vs 27.2 ± 2.3 kg/m²). Mean free testosterone concentration in diabetic cases was 3.34 ± 0.319 ng/dl which was significantly lower (P < 0.001) than the free testosterone concentrations in controls (mean value 10.64 ± 0.43 ng/dl). On the basis of usual normal ranges, 22 (44%) of 50 type 2 diabetic patients

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were hypogonadal, whereas out of 50 controls, only 4 (8%) were hypogonadal (P < 0.001). Testosterone levels were low in diabetic cases than controls in all age groups and this difference was statistically significant. Testosterone levels also fell as age of the patient increased (Table II). Out of 50 controls, 3 patients had BMI between 30 – 34.9 while 1 patient had BMI above 35 (mean BMI 23.5 ± 1.9 kg/m^2). Whereas 5 cases had BMI between 30 – 34.9 while 1 patient had BMI above 35 (mean BMI 27.3 ± 2.3 kg/m^2). In our patients, testosterone levels consistently fell as BMI of the patient increased. Levels of testosterone were significantly low in cases in all groups of BMI (P < 0.001) (Table III). Since testosterone concentrations decline with age normally also, we studied correlation of age with serum testosterone levels and found that testosterone levels had non-significant negative correlation with age (Table IV).

Table I: Comparison of demographics and biochemical profiles of controls and diabetic cases.

Parameters	Controls	Diabetic cases	P
Number	50	50	
Mean age	53.5 ± 4.38 years	52.4 ± 4.2 years	
BMI (kg/m^2)	23.5 ± 1.9	27.2 ± 2.3	
Free T levels (ng/dl)	10.64 ± 0.43	3.34 ± 0.319	
Hypogonadism (n)	4	22	< 0.001
% hypogonadism	8	44	< 0.001
Mean blood sugar levels (mg/dl)	FBS = 93 ± 12 PPBS = 125 ± 26	144 ± 39 256 ± 40	< 0.05

Table II: Distribution of testosterone levels in controls and diabetic cases in various age groups.

Age group	Controls (mean values of T in ng/dl)	Cases (mean values of T in ng/dl)	T value	P (statistical signifi-cance)	Inference
21-30	11.7 ± 2.2	9.3 ± 2.7	5	< 0.001	Highly significant
31-40	10.3 ±1.2	6.6 ± 1.1	16	< 0.001	Highly significant
41-50	9.2 ± 2.1	4.7 ± 2.2	10.4	< 0.001	Highly significant
51-60	8.1 ± 2.2	4.4 ± 2.3	8.44	< 0.001	Highly significant
61-70	6.8 ± 2.2	3.7 ± 2.2	7.07	< 0.001	Highly significant
Total (n)	**50**	**50**			

Table III: Distribution of testosterone (T) in controls and diabetic cases in relation to BMI.

BMI (kg/m^2)	Controls (mean values of T in ng/dl)	Cases (mean values of T in ng/dl)	T value	P (statistical signifi-cance)	Inference
< 20	12.3 ± 1.1	8.7 ± 0 .16	16.8	< 0.001	Highly significant
20-24.9	11.9± 2.2	7.8 ± 0.58	12.6	< 0.001	Highly significant
25-29.9	11.2 ± 1.9	7.6 ± 0.69	10.4	< 0.001	Highly significant
30-34.9	10.9 ± 1.1	6.96 ± 0.58	9.48	< 0.001	Highly significant
> 35	10.6 ± 0 .9	6.5 ± 0.55	8.87	< 0.001	Highly significant
Total (n)	**50**	**50**			

Table IV: Correlation of free testosterone (T) with age.

Parameter	Controls		Diabetics	
	Correlation (r)	P	Correlation (r)	P
Pts with low T levels (4)	0.088	.090 *	- 0. 260	0.243 *
Pts with normal T levels (44)	- 0.729	0.89 *	- 0.206	0.293 *
Total (50)	**0.099**	**1.933 ***	**- 1.112**	**0.441 ***

** not significant*

Discussion

Distribution of testosterone levels in various age groups in diabetic cases and controls

The prevalence of low testosterone levels was much higher than what was expected based on the age of subjects (Table II). Normal ageing is associated with a decrease in total testosterone levels of the order of 0.5 - 2% per year. The fall in testosterone is gradual and constant over all decades and starts early in life, probably after the third decade. The exact cause of the age-related reduction in testosterone levels is not known; it is probably the result of a combination of factors, including:-

- Increased abdominal fat, and therefore increased aromatase activity which converts testosterone into oestrogen.
- Age-related oxidative damage to testis and Leydig cells, resulting in decreased production of testosterone. Leydig cells are interstitial cells which

are interspressed between the seminiferous tubules of the testis. They secrete androgen in response to stimulation by luteinising hormone (LH) from the anterior pituitary gland.

- Declining levels of precursor molecules, such as dehydroepiandrosterone (DHEA). It is produced by the adrenal glands and is the precursor of the sex hormones oestrogen and testosterone.
- Nutritional status and liver function.
- Increased SHBG production.

Plotting free testosterone levels in various age groups (Table II) in controls and cases, showed that serum testosterone levels are significantly low in diabetic cases in all age groups. Our observations are in conformity to those of Dhindsa *et al*[6].

Testosterone biosynthesis is regulated primarily by pulsatile secretion of luteinising hormone (LH) and serum testosterone levels reflect the integrity of the hypothalamic-pituitary-gonadal (HPG) axis. Therefore low testosterone levels noted in cases of insulin resistance may indicate a defect at one or more functional levels of the HPG axis. In the insulin-resistance state, Leydig cell function, particularly steroidogenesis, may be impaired by changes in the production of hormones and cytokines locally in the target tissue and in adipose tissue. Although several studies suggest that increasing insulin resistance may be attributed to a decrease in testosterone secretion in men, it is not fully clear how the HPG axis mediates the interplay between testosterone and insulin levels. Other potential mechanisms for low testosterone levels in type 2 diabetes mellitus include reduced or absent stimulatory effect of insulin on Leydig cells[7], increased leptin levels in diabetes causing Leydig cell dysfunction[8], incresed TNF levels in diabetes inhibiting steroid biosynthesis in Leydig cells[9]. Clearly, additional studies are needed to fully delineate the biochemical and physiological mechanisms underlying reduced T synthesis in diabetes.

Mean testosterone levels tend to be lower with advancing age in diabetics and normal controls also, but this decline was statistically not significant (Table IV).

Distribution of testosterone (T) in controls and diabetics in relation to BMI

The data was then analysed after dividing patients into categories based on BMI (Table III): Testosterone levels fell progressively with increase in BMI, and the trend was significant across the groups. 13.5% of obese patients in our study had low testosterone levels. These findings were in conformity with the finding of Zumoff *et al*[10] and Vermeulen *et al*[11]. Obesity and associated hyper-insulinaemia suppress the action of luteinising hormone (LH) in the testis, which can significantly reduce circulating testosterone levels[12], even in men under the age of 40. The vicious circle of low testosterone and obesity has been described as the hypogonadal/obesity cycle. In this cycle, a low testosterone level results in increased abdominal fat, which in turn leads to increased aromatase activity. This enhances the conversion of testosterone to oestrogens, which further reduces testosterone and increases the tendency toward abdominal fat[13]. Thus, data from our study suggest that obesity/insulin-resistance is associated with hypogonadism and low testosterone levels.

However, the prevalence of hypogonadism in the normal BMI group was 36% versus 31.3% as seen by Dhindsa *et al*[6]. Thus, despite the relatively weak but significant inverse correlation of testosterone with BMI, low testosterone values were common in the normal BMI. Thus, although obesity may explain part of the high prevalence of hypogonadism, it is likely that other factors associated with type 2 diabetes also contribute significantly.

Conclusion

We therefore conclude from the present study that low testosterone level is a common defect in type 2 diabetes, irrespective of age and BMI of patients.

Further work is needed to assess whether testosterone deficiency in type II diabetes mellitus is responsible for this long-term complication of diabetes, and whether testosterone replacement therapy will be beneficial in these cases.

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ORIGINAL ARTICLE

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A study of sixty cases of chronic daily headache

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Abstract

Aims: To identify the clinical features of chronic daily headache (CDH), its associated symptoms and classification, and to study its effect on patients that leads to functional disability.

Study design: A prospective, cross-sectional study was done in 60 patients with chronic daily headache.

Material and methods: The study was conducted on 60 outdoor patients of the Department of Medicine at Shri Sayajirao General Hospital, Vadodara, Gujarat. The study included patients who were diagnosed to have chronic daily headache.

Conclusion: Chronic daily headache is a major cause of disability which can be managed successfully.

Key words: Chronic daily headache, headache syndromes, cephalgia.

Introduction

Headache is a symptom of a range of neurobiological disorders, including some of the most common and ubiquitous. Adults aged 20 - 50 years are the most likely sufferers, but children and adolescents are also affected[1].

The term headache disorder encompasses a number of conditions that vary in severity, incidence, and duration. Chronic daily headache (CDH) is not a diagnosis, but the presence of headache on at least 15 days a month for at least 3 months. Patients with CDH need secondary aetiologies to be excluded through appropriate investigations before starting treatment.

Aims of study

1. To identify the clinical features of chronic daily headache, the associated symptoms, and its classification.
2. To study the effect of disease on patients that leads to functional disability.

Material and methods

This study was carried out at Shri Sayajirao General (SSG) Hospital, Vadodara, Gujarat, between January 2010 and September 2011. The study was performed in 60 patients in the age group of 14 - 60 years who presented with typical headache not attributable to any organic cause.

Detailed history was taken and complete neurologic examination was done for all the study patients. Patients were assessed by an ophthalmologist and otorhinolaryngologist when indicated, and an opinion by a psychiatrist was obtained if a sleep disorder or depression was suspected.

Routine haematologic and biochemical investigations were done and neuro-imaging was done only in a few patients as most of them could not afford the same.

Inclusion criteria

1. Patients having headache for more than 15 days in a month with or without medications.
2. Patients having history of primary headache for a duration of at least 3 months.

Exclusion criteria

1. Patients with history suggestive of elevated intracranial pressure, focal neurologic deficit, or meningitis.
2. Patients with headache attributable to hypertension or refractive errors.
3. Patients with secondary causes of headache like trauma, vascular disorders, or substance abuse.

Results

This study revealed that chronic daily headache (CDH) affects the most productive age group (30 - 50 years), creating a significant impact on the family and society (Table I).

Out of 60 patients in the study, 22 were males and 38 were females (Table II).

The most common CDH in this study is migraine without

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aura while the least common type of headache is hemicrania continua (Table III).

48 out of 60 patients had unilateral headache. Out of these, 12 patients had pain in the occipital region, 15 had frontal region involvement, 12 had pain in the parietal region, and 9 patients had pain in the temporal region (Table IV).

Vertigo associated with headache was present in 35% patients. 50% of patients with chronic migraine had vertigo, and 40% patients with cluster headache had vertigo (Table V).

Associated aura (visual and auditory) was present in 26.66% of patients with headache. Among the patients with migraine, 30.76% had visual aura while 15.38% had sensory aura. 40% patients of cluster headache had visual aura (Table VI).

60% patients reported headache as a reason for disability in their life. 80% patients of cluster headache reported disability due to their headache, while 76.92% patients suffering from migraine cited migraine as a cause of disability in their life. Among the patients with tension type headache, 46.66% had disability due to headache while 23.07% patients of new daily persistent headache reported disability due to their headache (Table VII).

Work was the most common provoking factor for headache in 23% patients followed by noise with 13%. Among the patients with migraine, work was a provoking factor in 38.46%, and 26.92% patients reported noise as a provoking factor for headache. 80% patients with cluster headache had no provoking factor (Table VIII).

35% patients got relief from headache by taking rest, 18.33% patients got relieved by taking medication, and 15% patients got relief by local massage (Table IX).

Sleep duration of less than 6 hours was reported by 18.33% patients with CDH and 20% patients having cluster headache (Table X).

Table I: Age distribution of patients with chronic daily headache.

Type of headache		Age (in years)				
		10-20	20-30	30-40	40-50	50-60
Migraine	*Without aura*	5	7	5	1	0
	With aura	1	2	4	1	0
Tension type		1	1	5	6	2
New daily persistent		4	1	6	1	1
Cluster		0	2	2	1	0
Hemicrania continua		0	0	1	0	0

Table II: Gender distribution of patients with chronic daily headache.

Type of headache		Gender	
		Male	Female
Migraine	*Without aura*	6	12
	With aura	5	3
Tension type		3	12
New daily persistent		5	8
Cluster		2	3
Hemicrania continua		1	0

Table III: Different types of chronic daily headache.

Type of headache		Total number of patients	Percentage
Migraine	*Without aura*	18	30 %
	With aura	8	13.33 %
Tension type		15	25 %
New daily persistent		13	21.66 %
Cluster		5	8.33 %
Hemicrania continua		1	1.66 %

Table IV: Location of pain in chronic daily headache.

Type of headache		Area of brain affected			
		Occipital	Frontal	Parietal	Temporal
Migraine	*Without aura*	4	6	2	6
	With aura	1	3	4	0
Tension type		2	1	2	2
New daily persistent		3	3	3	0
Cluster		1	2	1	1
Hemicrania continua		1	0	0	0

Table V: Associated vertigo in chronic daily headache.

Type of headache		Vertigo	
		Yes	No
Migraine	*Without aura*	8	9
	With aura	5	4
Tension type		3	12
New daily persistent		3	10
Cluster		2	3
Hemicrania continua		0	1

Table VI: Associated aura in chronic daily headache.

Type of headache	Aura		
	Visual	Sensory	No aura
Migraine	9	5	13
Tension type	2	0	12
New daily persistent	0	0	13
Cluster	2	0	3
Hemicrania continua	0	0	1

Table VII: Disability in chronic daily headache.

Type of headache		Disability	No disability
Migraine	*Without aura*	13	5
	With aura	8	0
Tension type		7	8
New daily persistent		3	10
Cluster		4	1
Hemicrania continua		1	0

Table VIII: Provoking factors in chronic daily headache.

Type of headache		Provoking factor				
		Stress	Work	Noise	Others	None
Migraine	*Without aura*	2	8	5	3	0
	With aura	2	2	2	1	1
Tension type		1	1	1	1	11
New daily persistent		0	2	0	4	6
Cluster		0	0	0	1	4
Hemicrania continua		0	0	0	1	0

Table IX: Relieving factors in chronic daily headache.

Type of headache		Relieving factor			
		Rest	Medication	Local massage	None
Migraine	*Without aura*	9	2	2	3
	With aura	6	3	0	0
Tension type		6	1	3	6
New daily persistent		2	3	2	6
Cluster		2	2	1	0
Hemicrania continua		0	0	1	0

Table X: Sleep association in chronic daily headache.

Type of headache		Duration of sleep	
		< 6 hours	> 6 hours
Migraine	*Without aura*	5	13
	With aura	0	8
Tension type		1	14
New daily persistent		2	11
Cluster		1	4
Hemicrania continua		1	0

Discussion

Chronic daily headache (CDH) affects 4% of adults and has a higher prevalence in females. There is no underlying organic pathology in CDH. The headache is reported as lasting 24 hours per day, 7 days in a week, waxing and waning with the pain, characterised as band-like or crushing and holocephalic.

Chronic Daily Headache can be divided into 5 groups:-

1. Chronic migraine.
2. Hemicrania continua.
3. New-onset daily persistent headache.
4. Chronic tension-type headache.
5. Cluster headache.

Before establishing a diagnosis of CDH, life-threatening causes of headache should be ruled-out with the help of neuro-imaging[2]. Symptoms suggestive of life-threatening causes of headache are:-

1. Presence of neurologic signs like seizures, confusion, impairment of sensorium, or papilloedema.
2. Presence of fever with neck rigidity.
3. Worsening of pre-existing headache.
4. Headache in an immune-compromised host.

The common types of CDH in clinics are chronic migraine (78%) and chronic tension-type headache (15%)[3]. Nearly all migraine sufferers and 60% of those with tension-type headache experience a reduction in social activities and work capacity[4].

Migraine has a variable prevalence worldwide. 12% of the general population have regular attacks of migraine. More women are affected by migraine than men in a ratio of 23:1[5].

The onset of tension-type headache is in the teenage years and its prevalence peaks in the fourth decade and then declines. Tension-type headache is also more common in women, in a ratio of 1.5:1[5].

The World Health Organisation (WHO) places migraine among the world's top 20 leading causes of disability[6]. The WHO recognition of migraine and other headache disorders as a major global disorder is a big step towards relieving the burden of headache around the world.

Limitations

1. Exact incidence of headache and their subtypes could not be estimated as this study involved a random selection of patients coming on one day of the week.
2. All patients could not undergo a CT scan of the head which is necessary to rule-out secondary causes like hydrocephalus or vascular/non-vascular causes of headache.

Conclusion

Health economic studies have documented that the costs of headache disorders are huge. The cost of migraine management amounts to approximately 27 billion euros in the European Union countries. However, better population-based cost studies are needed to assess the cost involved with tension-type headache. Migraine leads to a high degree of disability with forced absence from work and leisure activities. In addition, there is a marked impact on family life with considerable strain being put on the partners and children of sufferers.

This study has identified some of the main domains of headache in order to capture as much as possible of the burden of headache.

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ORIGINAL ARTICLE

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A study of fraction of exhaled nitric oxide levels as a diagnostic marker in patients with bronchial asthma

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Abstract

Aim: To compare the fraction of exhaled nitric oxide (FENO) levels in patients with and without bronchial asthma and correlate the FENO level with steroid therapy and severity of bronchial asthma.

Study design: A cross-sectional case control study of 55 cases of bronchial asthma and 45 controls.

Materials and methods: Fifty-five cases of bronchial asthma and 45 controls with identical demographic characteristics, having respiratory diseases other than asthma but not on steroids were studied and compared. Computerised spirometry studies and FENO levels measurement by chemiluminiscence NO-analyser was performed in both the groups and compared. The data was analysed using SPSS software.

Results: The mean FENO levels were significantly higher in asthmatics [16.5 parts per billion (ppb)] as compared to non asthmatics (5.5 ppb). The sensitivity of FENO in making a diagnosis of asthma was 72% and the specificity 88%. The mean FENO levels were significantly higher in both steroid treated cases (15.7 ppb) and steroid naïve cases (41.5 ppb) as compared to controls (14.4 ppb). The mean FENO level increases as the severity of asthma increases in both steroid treated (mild-6.3, moderate-15.1, severe-18.8 ppb) and steroid naïve cases (mild-11.9, moderate-20.7, severe 28.9 ppb). The FENO levels were lower in steroid treated cases as compared to steroid naïve cases, however the difference was not statistically significant.

Conclusion: FENO levels are elevated in bronchial asthma and have a sensitivity of 72% and specificity of 88% as a diagnostic marker. FENO levels significantly correlate with the severity of asthma and the levels reduce with steroid therapy.

Key words: FENO, bronchial asthma, steroid therapy, diagnostic marker.

Introduction

Wheeze, shortness of breath and cough, variable in severity, and over time, characterise bronchial asthma. Since long-term inhaled corticosteroids form the mainstay of treatment of bronchial asthma, it is preferable to validate the diagnosis with objective tests[1]. The traditional approach to the diagnosis of bronchial asthma like serial peak expiratory flows, spirometry, response to inhaled bronchodilator or a trial of corticosteroid are primarily based on demonstrating abnormal airway physiology, which may often not be present in mild asthma. Hence the sensitivity of these tests is low[1].

Secondly, obtaining peak flow recordings or repeated spirometry may be difficult due to inadequate patient compliance[2] and since the spirometry procedure is effort dependent, many subjects may be unable to perform the procedure. Alternative laboratory-based test for bronchial hyper-responsiveness (BHR) such as methacholine challenge test has been tried. But the sensitivity of these tests are variable. Moreover, they may not be readily accessible[3,4] and the patient may have severe bronchospasm.

Fraction of exhaled nitric oxide (FENO) measurement has been highlighted in recent studies as a potential diagnostic tool for non invasive assessment of asthmatic airway inflammation[1,5] in asthmatics. FENO has a high degree of discriminatory power to differentiate asthmatic from non- asthmatic patients[1]. Nitric oxide is produced by a variety of cells involved in asthma, the highest output being from epithelial cells and macrophages. Nitric oxide produces a chemiluminescence on reaction with ozone which is used to measure FENO levels in various studies[6]. Thus FENO which measures abnormal airway pathology is probably a better diagnostic tool than the traditional approaches based on abnormal physiology[7]. This study has been planned to study FENO levels as a diagnostic marker of bronchial asthma and to study the effect of steroid therapy on FENO levels.

Aims and objectives

- To compare FENO levels in patients with and without bronchial asthma.
- To study the correlation of FENO levels with severity of bronchial asthma.

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- To compare FENO levels in steroid treated asthmatics with those of steroid naïve asthmatics.

Materials and methods

This cross-sectional case control study was conducted in KMC group of hospitals, Mangalore, Manipal University. Fifty-five patients having bronchial asthma as per GINA 2009 guidelines[8] were included as cases and 45 patients having respiratory illnesses other than bronchial asthma were taken as controls. Patients with chronic respiratory illness like COPD, bronchiectasis, cystic fibrosis, and patients on steroids were excluded from the control group. All the patients were clinically evaluated with history and examination. Computerised spirometry was performed for each subject using P. K. Morgan spirometry, and pulmonary function tests were done by a trained technician as per ATS standard guidelines[9]. The cases were classified into mild, moderate, and severe asthmatics depending on the level of asthma control as per GINA 2009 guidelines[8], wherein controlled asthma as mild, partially controlled as moderate, and uncontrolled as severe asthma. Three FENO measurements were recorded for each subject using chemiluminescence NO-analyser and the procedure was performed as per standard recommendation. Repeat measurements were performed until the three values agreed to 10% of the mean. Mean value of the 3 measurements was recorded as final. FENO level of < 8.0 ppb was taken as normal.

Analysis

The data was collected and descriptive analysis of the data was done using Microsoft Excel spread sheets and SPSS software.

Results

The study comprised of 55 cases and 45 controls. Of the 55 cases, 28 were on inhalational steroids, whereas the remaining 27 were steroid naïve. Minimum age for cases and controls was 12 and 16 years respectively. Maximum age for cases and controls were 82 and 76 years respectively. Out of 55 cases 23 were males and 32 were females. Out of 45 controls, 22 were males and 23 were females. The mean age in the cases and controls was 45.2 and 48.5 respectively. The mean age of all the subjects was 46.7. The cases and controls were matched for age and sex. [T value .919, P value = 0.36 (not significant)].

The mean FENO levels were significantly higher in asthmatics as compared to non-asthmatics (Table I). The sensitivity of FENO in making a diagnosis of asthma is 72% and the specificity is 88%. In the steroid treated group, the sensitivity was 75%, and in the steroid-naive group sensitivity was a bit lower at 70%. Since steroid therapy is known to bring down FENO levels, one would expect the sensitivity to be lower in the steroid-treated group, rather than in the steroid-naive group. However, our results can be explained by the fact that, the severity of asthma was much higher in the steroid-treated group, thus contributing to higher FENO levels.

The mean FENO levels were significantly higher in both steroid treated and steroid naive cases as compared to controls (Table II). There is a significant correlation between the severities of asthma in steroid treated cases with FENO levels. That is, as the asthma worsens there is a corresponding increase in FENO levels (Table III). The FENO levels significantly correlate with the severity of asthma in steroid naïve cases as well (Table IV). The FENO levels were lower in steroid treated cases as compared to steroid naïve cases. However this reduction in FENO levels with steroid therapy was not statistically significant (Table V).

Discussion

It is now 18 years since it was first reported that exhaled nitric oxide (NO) levels are increased in bronchial asthma. This discovery followed a period of intense interest in the biology of NO during the late 1980s. The numerous roles of NO in respiratory pathophysiology have been extensively reviewed. NO is an endogenous messenger with a diverse range of effects including non-adrenergic, non-cholinergic neurotransmission, vascular and non-vascular smooth muscle relaxation. There is contradictory evidence regarding the exact function of NO in lung disease. In pathological situations NO is a pro-inflammatory mediator with immunomodulatory effects. This appears to predispose to the development of airway hyper-responsiveness (AHR), although this is not a consistent finding. On the other hand, under physiological conditions, NO acts as a weak mediator of smooth muscle relaxation and protects against AHR. In exhaled air NO appears to originate in the airway epithelium. Although raised levels may occur with a number of airway or lung diseases, the most important context in which the measurement of NO is clinically useful is that of allergic airway disease. It is against this background that measuring the fraction of NO in exhaled air has emerged as a potentially important clinical tool. FENO can be measured easily using a range of commercially available analysers, and smaller less costly devices are now becoming available. This opens the possibility that FENO measurements might be used routinely in the assessment of airway disease. This is a significant advance. To date, assessing airway physiology, that is, changes in airway

calibre and/or bronchodilator or bronchoconstrictior responsiveness has been the principal means of providing supportive evidence for the diagnosis of airways disease and assessing severity. Although pulmonary function tests will always remain important, they are one step removed from the issue of interest that is, airway inflammation. Thus, FENO measurements provide a complementary and, in some instances, a more relevant perspective.

Table I: FENO in cases vs. controls (in parts per billion).

Group	Number	Minimum FENO	Maximum FENO	Mean FENO	Std. deviation	Median	Mann-Whitney test Z value
Cases	55	2.0	41.5	16.5	10.3	15.0	5.81
Controls	45	2.0	14.4	5.5	2.7	5.4	
Total	**100**	**2.0**	**41.5**	**11.5**	**9.5**	**7.0**	

p value < 0.001 (highly significant)

Table II: FENO in steroid-treated and steroid-naive cases vs. FENO in controls (in parts per billion).

Group	Number	Minimum FENO	Maximum FENO	Mean FENO	Standard deviation	Mann-Whitney test Z value
Steroid-treated cases	28	3.3	39.6	15.7	9.8	5.26
Controls	45	2.0	14.4	5.5	2.7	
Steroid-naive cases	27	2.0	41.5	17.3	10.9	4.36
Controls	45	2.0	14.4	5.5	2.7	

p values < 0.001 (highly significant)

Table III: Correlation of FENO with severity of asthma in steroid-treated cases.

Severity of asthma	Number	Minimum FENO	Maximum FENO	Mean FENO	Standard deviation	Median	Kruskal-Wallis test value
Mild	5	3.3	10.6	6.3	2.6	5.9	8.57
Moderate	7	4.4	32.6	15.1	9.7	14.1	
Severe	16	7.0	39.6	18.8	9.7	16.8	

p value = 0.014 significant

Table IV: Correlation of FENO with severity of asthma in steroid-naïve cases.

Severity of asthma	Number	Minimum FENO	Maximum FENO	Mean FENO	Standard deviation	Median	Kruskal-Wallis test value
Mild	15	2.0	25.2	11.9	8.3	12.2	9.09
Moderate	7	6.6	32.0	20.7	8.2	20.4	
Severe	5	14.1	41.5	28.9	11.3	32.0	
Total	**27**	**2.0**	**41.5**	**17.3**	**10.9**	**18.7**	

p value = 0.011 (significant).

Table V: Comparison of FENO in steroid-treated cases vs. steroid-naïve cases.

Severity of asthma	Steroid therapy	No.	Minimum FENO	Maximum FENO	Mean FENO	Standard deviation	Mann-Whitney test value	p value
Mild	Yes	5	3.3	10.6	6.3	2.6	1.13	0.25 (NS)
	No	15	2.0	25.2	11.9	8.3		
Moderate	Yes	7	4.4	32.6	15.1	9.7	1.21	0.22 (NS)
	No	7	6.6	32.0	20.7	8.2		
Severe	Yes	16	7.0	39.6	18.8	9.7	1.81	0.06 (NS)
	No	5	14.1	41.5	28.9	11.3		

Recent studies have shown the role of FENO in the diagnosis of bronchial asthma and its ability to distinguish asthmatic from non-asthmatic subjects[1,5]. FENO being a measure of abnormal airway pathology seems to be more appropriate in the diagnosis of asthma as compared to the traditional approaches based on abnormal physiology.

In this study we have attempted to validate FENO as a diagnostic tool of bronchial asthma and correlate the FENO levels with the severity of asthma. We also compared the FENO levels in steroid-treated and steroid-naïve asthmatics. Our study compared the FENO levels in asthmatic patients with those in controls. Unlike the studies conducted by Deykin *et al*[5] and by Zietkowski *et al*[10], patients on steroids were not excluded from the study. The control arm in our study consisted of a variety of patients suffering from respiratory diseases like tuberculosis, interstitial lung disease, etc. We found a highly significant correlation between the diagnosis of asthma and elevation of FENO levels in both the groups, i.e, steroid-treated and steroid-naive groups ($p < 0.001$)(Table I, II).

Deykin *et al*[5] and Zietkowski *et al*[10] used GINA guidelines to diagnose asthma in their study. Deykin *et al*[5]and Zeitkowski *et al*[10] found highly significant correlation of asthma with elevated FENO levels ($p < 0.001$), as also was concluded in our study.

Tsujino *et al*[11] used the National Heart, Lung and Blood Institute guidelines to diagnose asthma in their study. Steroid treated asthmatics were also included. They found a significant correlation of asthma with FENO levels ($p < 0.05$). They also found that there was no significant difference in FENO levels in patients with COPD and bronchiectasis, as compared to healthy controls.

Our findings correlate with Tsujino's study, except that the difference in FENO levels in steroid-treated and steroid-naive asthmatics is much lower in our study. This might be related to the difference in the dose of steroids taken by the patients. In our study, the sensitivity of FENO to make a diagnosis of asthma was 72%, and specificity was 88%.

According to Smith *et al*[1] FENO was 88 % sensitive, and 79 % specific in making a diagnosis of asthma. However, the definition of asthma used in Smith's study was different in that they followed American Thoracic Society criteria, which rely on bronchial hyper-responsiveness and post-bronchodilator reversibility, as against our study which used FEV1 and post-bronchodilator reversibility.

In the study by Kostikas *et al*[15], the modified European Community Respiratory Health Survey questionnaire was used to define asthma. They found FENO 85.2 % sensitive and 52.4 % specific as a diagnostic marker for asthma. It thus follows that the sensitivity and specificity of FENO as a diagnostic marker depends significantly on the criteria used to define asthma.

In our study, to correlate the FENO levels with the severity of asthma, we divided the cases into mild, moderate, and severe asthmatics, as per the GINA 2009[8] guidelines, which rely on symptomatology, FEV1, and post-bronchodilator reversibility. It was modified slightly, wherein controlled asthma as mild, partially controlled as moderate, and uncontrolled as severe asthma. Here, there was a confounding factor – as the severity of asthma increased, the proportion of the patients on steroid therapy increased. This tends to bring down the average FENO levels in severe asthmatics, as most were on steroid treatment. To overcome this, we first divided the cases into steroid-treated and steroid-naive asthmatics. Thereafter, we classified each group into mild, moderate, and severe asthmatics. The correlation of FENO levels with the severity of asthma was studied separately in both the groups, i.e, the steroid-treated group and the steroid-naive group. We found a significant correlation between FENO levels and the severity of asthma in both steroid-naive and in steroid-treated patients, i.e., as the severity of asthma increases, there is a corresponding increase in the FENO levels as well (Table III, IV).

Tsujino *et al*[11] also correlated the severity of asthma with FENO levels separately for steroid-treated and steroid-naive groups, like in our study. They found significant correlation only in the steroid-naive group ($p < 0.05$), but not in the steroid-treated group. This is probably because the steroid doses (mean dose 775 mcg beclomethasone) were probably higher in Tsujino's study compared to ours. In our study, the patients were on different inhalational steroids, and so average dose could not be calculated.

We also studied the effect of steroid therapy on FENO levels in our study. We compared the FENO levels in steroid-treated patients with those of steroid-naive patients, separately in mild, moderate, and severe asthmatics. We found that the mean FENO levels were lower in the steroid-treated group in all three groups, and the difference was greater as the severity of asthma increased. But the p values were not significant, ($p = 0.25$ for mild asthma, 0.22 for moderate asthma, and 0.06 for severe asthma). This is probably due to small sample size studied. For example, among mild asthmatics ($n = 20$), only 5 were steroid-treated. However, in the severe asthmatics group, where the FENO levels in the steroid-naive subjects were much higher, the p value was close to being significant ($p = 0.06$) (Table V). According to Tsujino *et al*[11] and Verleden *et al*[16] there was a significant decrease in FENO levels with steroid therapy ($p < 0.05$).

Kharitonov *et al*[17] conducted a study exclusively to study

the effect of steroid therapy on FENO. They found that FENO levels were inversely proportional to the dosage of budesonide ($p < 0.05$).

The limitations of our studies are:-

Firstly, the in-homogeneity in the steroid arm as patients were receiving various groups, different strength of steroids and other controller medicines. Secondly, sputum eosinophilia which is another non-invasive marker for airway inflammation was not done in our study. Thirdly, to study the effect of FENO and its relation to dose of inhaled steroids, probably a longer duration of study and serial FENO measurements would have been useful.

International guidelines for the treatment of asthma recommend adjusting the dose of inhaled corticosteroids on the basis of symptoms, bronchodilator requirements, and the results of pulmonary function tests. Measurements of the fraction of exhaled nitric oxide (FENO) constitute a non-invasive marker that may be a useful alternative for the adjustment of inhaled-corticosteroid treatment. Since in our study the FENO levels correlate well with the severity of asthma and the maintenance dosage of steroids used for the level of severity, we suggest FENO could be used as a surrogate marker for dose titration of inhaled steroids. The use of exhaled nitric oxide measurements (FENO) in clinical practice is now coming of age. There are a number of theoretical and practical factors which have brought this about. Firstly, FENO is a good surrogate marker for eosinophilic airway inflammation. High FENO levels may be used to distinguish eosinophilic from non-eosinophilic pathologies. This information complements conventional pulmonary function testing in the assessment of patients with non-specific respiratory symptoms. Secondly, eosinophilic airway inflammation is steroid responsive. There are now sufficient data to justify the claim that FENO measurements may be used successfully to identify and monitor steroid response as well as steroid requirements in the diagnosis and management of airways disease. FENO measurements are also helpful in identifying patients who do/do not require ongoing treatment with inhaled steroids. Thirdly, portable nitric oxide analysers are now available, making routine testing a practical possibility. However, a number of issues still need to be resolved, including the diagnostic role of FENO in pre-school children, the use of reference values versus individual FENO profiles, role of FENO in acute exacerbations and in managing patients with difficult or severe asthma.

Conclusions

- FENO levels are elevated in patients with bronchial asthma.
- For making a diagnosis of asthma, the sensitivity and specificity of FENO levels is 72 % and 88 % respectively.
- FENO levels are significantly correlated with the severity of asthma, in steroid-naive as well as in steroid-treated patients.
- FENO levels come down with steroid therapy in asthmatics. However, this reduction was not statistically significant.

Ethical consideration

Informed consent was obtained from each subject or from his/her guardian.

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ORIGINAL ARTICLE

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Association of abdominal fat with blood pressure in normal healthy subjects

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Abstract

The role of obesity in many disorders is well established. Research has shown that the location of body fat deposits is a more important determinant than the size of these deposits in developing obesity related disorders. The role of body fat distribution has received limited attention. We determine the relationship between distribution of body fat and blood pressure. Specifically to measure subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) and to correlate them with blood pressure (systolic and diastolic). Sixty normal subjects (mean age 30.38 ± 5.44 yrs., 28 males, and 32 females), after exclusion criteria were selected. Parameters such as subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) and blood pressure of all the subjects were measured. SAT and VAT were detected by ultrasonography (5 MHz) and blood pressure was recorded with a standard sphygmomanometer. Statistical analyses were carried out using Pearson's correlation. The study participants had a mean (± SD) age of (30.38 ± 5.44 years). The mean systolic and diastolic blood pressures were (120.42 ± 4.55 mmHg) and (78.00 ± 5.13 mmHg) respectively. With regard to fat parameters, mean SAT was (1.67 ± 0.58 cm) and mean VAT was (3.67 ± 0.85 cm). All of these parameters showed no significant difference (p > 0.001). A high significant positive correlation was observed between SAT and SBP (0.498, p < 0.001) whereas weak significant correlation was observed between SAT and DBP (0.291, p < 0.018) whereas the correlation between VAT and SBP was found significant (0.330, p < 4.9121). The study concluded that subcutaneous abdominal adipose tissue is a better parameter than visceral abdominal adipose tissue that correlates with blood pressure in normal subjects.

Key words: SAT, VAT, blood pressure.

Introduction

Obesity is defined as excessive accumulation of fat in the body and is the most common nutritional disorder in humans. It is a major cause of mortality and morbidity for associated metabolic disorders and cardiovascular disease. With regard to the risk of developing obesity-related disorders in general, extensive research[1, 2] has shown that the location of body fat deposits is a more important determinant than the size of these deposits. It has been shown that the presence of intra-abdominal visceral fat (VAT) in the mesentery and omentum is a better predictor of coronary heart disease, than the body mass index (BMI)[3].

The role of body fat distribution has received limited attention. Studies have shown that subcutaneous abdominal adipose tissue (SAT) and visceral abdominal fat are associated with blood pressure. But which of these is a better parameter that correlates with blood pressure in normotensive subjects is not clear[4,5]. So the aim of the study is to measure SAT and VAT by ultrasonography and to correlate them with blood pressure in normal subjects.

Material and method

The study was conducted in the departments of Physiology and Radiology at Subharti Medical College and associated hospital of the Swami Vivekanand Subharti University, Meerut, Uttar Pradesh. It is a cross-sectional study. Participants underwent the study voluntarily and provided written informed consent prior to inclusion in the study and the study protocol was approved by the ethics committee of the university.

The study comprised 60 normal subjects (28 males, 32 females, mean age 30.38+5.44 years) attending OPD for general check-up. Subjects who were known cases of hypertension, diabetes, coronary heart disease, stroke, chronic renal failure, chronic alcohol abuse and those who were on cholesterol lowering medication were excluded from the study.

All the subjects were examined for exclusion and inclusion criteria and suitable subjects were considered. The clinical examination included a detailed history regarding any addiction e.g., smoking and alcohol, and it was followed by a thorough systemic examination. Blood pressure was recorded in the sitting position three times with 5-minute intervals on the left arm with a standard sphygmo-manometer, and the average of three recordings was considered. SAT and VAT measurements were taken 1 cm above the umbilicus by ultrasonography (5 MHz) in the supine position. SAT is measured from the anterior

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abdominal wall to rectus sheath. VAT is measured from the rectus sheath to the anterior abdominal aorta[6,7].

Statistical analysis

Statistical analysis were carried out using Pearson's correlation analysis to assess the degree of relationship of study parameters with systolic and diastolic blood pressure and multivariate linear regression analysis to assess the prediction efficiency of the study parameters with systolic and diastolic blood pressure.

Results and discussion

This cross-sectional study was designed to determine subcutaneous abdominal tissue and visceral abdominal tissue in normal subjects. The purpose was to correlate them with blood pressure. We found that subcutaneous abdominal adipose tissue is a better parameter than visceral abdominal adipose tissue that correlates with blood pressure in normal subjects.

Table I shows age (years), SAT and VAT (cm), SBP and DBP (mmHg), in the form mean ± SD At base line, the study participants had a mean ± SD age of 30.38 ± 5.44 years. The mean systolic and diastolic blood pressures were 120.42 ± 4.55 mmHg and 78.00 ± 5.13 mmHg respectively. With regard to fat parameters, mean SAT was 1.67 ± 0.58 cm and mean VAT was 3.67± 0.85 cm. all of these parameters were studied on 60 subjects, showed no significant difference.

Table I: Various study parameters.

Study parameters	All cases		SEM
	Mean	SD	
Age (years)	29.94	1.7757	0.70
SAT (cm)	1.604	0.1656	0.07
VAT (cm)	3.59	0.1618	1.0
SBP (mmHg)	118.72	3.7902	0.57
DBP (mmHg)	80.94	4.3061	0.66

Table II shows correlation between blood pressure (viz. SBP and DBP) and fat parameter (viz. SAT and VAT). A high positive correlation was observed between SAT and SBP (0.516), whereas weak correlation was observed between VAT and DBP (0.110). Correlation between VAT and DBP was not significant ($p > 0.001$) whereas the correlation between VAT and SBP was found significant ($p < 0.05$) and correlation between SAT and SBP was found highly significant ($p < 0.001$).

Table 2: Correlation between blood pressure and fat parameters

Study parameters	SBP (mmHg)		DBP (mmHg)	
	Pearson correlation	Significance	Pearson correlation	Significance
SAT (cm)	0.498	< 0.001**	0.291	0.018*
VAT (cm)	0.330	4.9121*	0.125	0.413

Conclusion

This cross-sectional study was designed to determine subcutaneous abdominal tissue and visceral abdominal tissue in normal subjects. The purpose was to correlate them with blood pressure. We found that subcutaneous abdominal adipose tissue is a better parameter than visceral abdominal adipose tissue that correlates with blood pressure in normal subjects.

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"Real hearty, healthy smiles bring down blood pressure and make for long life. I think when humour disappears, humans are also finished."

– Frantisek Dostal.

ORIGINAL ARTICLE

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Clinical profile and risk factors in acute coronary syndrome

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Abstract

A prospective study was carried out to identify the risk factors and to know the emerging clinical profile in acute coronary syndrome (ACS) including ST elevation and non ST elevation myocardial infarction. We enrolled 200 patients with clinical history, ECG changes and troponin T positive, admitted in the intensive care unit at UP RIMS & R, Saifai, Uttar Pradesh, over a period of three years – April 2008 to April 2011.

A predefined pro forma was completed in every patient with a detailed clinical history, physical examination, and investigation studies. The clinical history revealed information about age, gender, risk factors, modes of presentation, and duration of symptoms.The details of physical examination including anthropometric data, vital signs and complete systemic evaluation were recorded. The regions of infarction and rhythm disturbances were also documented.Our study showed a significant male predominance with the mean age being 55 years. Tobacco was identified as a major risk factor (67%) and obesity (BMI more than 25) is the least common risk factor (12%). Patients had typical chest pain (90%), troponin T positive (100%), and ECG showed specific changes suggestive of ACS in 100%. Thirty per cent patients developed complications, majority being arrhythmias (63%) and least common is mechanical complication (4%)Thus we conclude that ACS is more common in late middle-aged (51 to 60 years) males with tobacco being a major risk factor in western UP rural population.

Key words: Coronary artery disease, tobacco, arrhythmia, acute coronay syndrome, chest pain.

Introduction

It is predicted that more than half the worldwide cardiovascular disease risk burden will be borne by the Indian subcontinent in the next decade according to recent epidemiological studies[1,16]. There are significant differences in the prevalence of coronary artery disease with respect to gender, age, and ethnicity. Cardiovascular disease has emerged as a major health burden in developing countries[2,17,21,22]. Cardiovascular risk factors for acute coronary syndrome (ACS) are on the rise in people of Indian origin, and ACS is now the leading cause of death[3,4 ,18,19,20].

Methodology

The study is conducted at our tertiary care institute – UP Rural Institute of Medical, Sciences & Research, Saifai, Etawah, Bundelkhand, Uttar Pradesh. The study was designed to take a sample size of 200 consecutive cases of acute coronary syndrome (according to ACC/AHA guidelines) during a period of 3 years from April 2008 to April 2011. It is a cross-sectional study. All the patients were examined and interviewed during their hospital stay. All the information was filled-up in a specially prepared pro forma.

Results

200 consecutive patients presenting with features of acute coronary syndrome were studied. These patients were predominately male (75%) with male to female ratio being 3:1.

The age range is between 31 to 81 years and the average age is 55 years as shown in Table I.

Table I: Age and sex wise distribution of cases of ACS.

S. No.	Age interval (years)	Male (%)	Female (%)
1.	31 - 40	14 (7)	4 (2)
2.	41 - 50	28 (14)	6 (3)
3.	51 - 60	56 (28)	16 (8)
4.	61 - 70	38 (19)	18 (9)
5.	71 - 80	14 (7)	6 (3)
Total	Males: 150 (75%),	Female: 50 (25%)	

The commonest presenting symptom was chest pain (90%),followed by sweating (75%) and breathlessness (60%) (Table II).

Table II: Distribution of presenting symptoms of ACS.

S. No.	Symptoms	No. of patients (%)
1.	Chest pain	180 (90)
2.	Sweating	150 (75)
3.	Breathlessness	130 (60)
4.	Palpitation	112 (56)
5.	Giddiness	70 (35)
6.	Vomiting	20 (10)
7.	Abdominal pain	8 (4)

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Tobacco consumption is a major risk factor in our present study (65%), hypertension (33%), diabetes mellitus (16%), family history of coronary artery disease (14%), obesity (13%), and dyslipidaemia (12%).

Table III: Distribution of selected risk factors.

S. No.	Risk factor	No. of patients (%)
1.	History of tobacco consumption in any form	130 (65)
2.	History of hypertension	66 (33)
3.	History of diabetes mellitus	64 (32)
4.	Family history of CHD	28 (14)
5.	Obesity	26 (13)
6.	Dyslipidaemia	24 (12)

Table IV: Distribution of troponin T positive cases according to site of ischaemia/infarction.

S. No.	Site of infarction on ECG	No. of patients (%)
1.	Anterior wall	100 (50)
2.	Inferior wall	80 (40)
3.	Global (combined) wall	10 (5)

It is observed that maximum number of patients (50%) had anterior wall involvement.

Table V: Distribution of cases according to complications.

S. No.	Complications	No. of patients (n=50) (25%)
1.	Arrhythmias	25 (50)
2.	Cardiac failure	20 (40)
3.	CVA	3 (6)
4.	Mechanical complication (VSD, MR, PMD)	2 (4)

(In our study, 50 patients (25%) developed complications in form of arrhythmia – 25, (50%), cardiac failure – 20 (40%), CVA – 3 (6%) and mechanical complication like VSD, MR, and PMD in 2 (4%)[4,15].

Discussion

Heart disease is the fatal cause of death more common in late middle-aged males and smoking is the major risk factor. In the present study, maximum number of cases of ACS were in the age group 51 to 60 (32%) – the cases were predominately male (75%) suggesting that it is predominately a disease of men[5,6]. The present study shows that with increasing age the preponderance of male patients admitted with ACS decreases and sex ratio becomes smaller.This possibly reflects a higher percentage of females, and elderly population, and more equal distribution of risk factors for ACS in both genders at higher age group[7,8]. Our study also showed that anterior wall myocardial infarction is common site of presentation (50%) as seen in the study of Deshpandey and Dixit[9]. The clinical presentation of cases in the of present study showed chest pain as a predominant symptom (90%) followed by sweating (75%), and breathlessness (60%). Other non specific symptoms like abdominal pain, giddiness, and syncope were observed in the higher age group as observed in the Yang *et al* study[10].

Smoking was the leading risk factor (65%); male preponderance and smoking being the major risk factor as seen in the study by Yusuf *et al*[11]. Diabetes alone was a risk factor in 32%, and hypertension alone in 33%. Diabetes mellitus is well known to have an adverse influence on the prognosis of patients with ACS as noted in the Hasdai *et al* study[12] In our study, 50 patients (25%) developed complications in form of arrhythmia – 25 (50%), cardiac failure – 20 (40%), CVA – 3 (6%), and mechanical complications like VSD, MR, and PMD in 2 (4%)[13,14,15].There are several limitations of this study as medium and long-term outcomes of these patients are not available.

Conclusion

In spite of the limitations highlighted above, it seems reasonable to draw some conclusion about the emerging profile of the patients presenting with ACS. Amongst the western UP, rural Indian population, most common sufferers of ACS are late middle-aged males. Cigarette smoking is the major risk factor. Anterior myocardial infarction is the most common. The majority of patients presented with typical symptoms of chest pain in a stable haemodynamic status and complications were noted in 25% cases.

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"The march of science has handed us such bonuses in health and energy and life-span that we should be living hugely, with enormous gusto and enjoyment, not tiptoeing through the years as if we were treading on eggs."

– Arthur Gordon.

ORIGINAL ARTICLE

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A comparative study of bone marrow aspiration and bone marrow biopsy in haematological and non haematological disorders – An institutional experience

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Abstract

***Objectives:** To correlate the bone marrow aspiration and bone marrow biopsy findings in haematological and non haematological disorders.*

***Study design:** Prospective study, setting: A tertiary care hospital in Shimla, Himachal Pradesh.*

***Subjects:** 460 patients above the age of 18 years were studied for haematological and non haematological disorders by both bone marrow aspiration and bone marrow biopsy.*

***Results:** Out of the 460 cases, 359 (78%) examinations provided either the diagnosis or diagnostic clues. Bone marrow aspiration findings correlated well with those of biopsy in 94% of the cases. In the remaining, trephine bone marrow biopsy was required to give the diagnosis. These cases were mostly of hypoplastic/aplastic marrow, NHL infiltration, myeloproliferative disorders, granulomatous and metastatic lesions.*

***Conclusion:** The decision to do the bone marrow aspiration or bone marrow biopsy depends upon the clinical situation. Most of the cases of nutritional anaemia, haematological malignancies, myeloproliferative disorders, multiple myeloma, and leishmianasis can be diagnosed by bone marrow aspiration alone.*

Introduction

Bone marrow examination is useful in the diagnosis of both haematological and non haematological disorders.

Indications have included the diagnosis, staging, and therapeutic monitoring for lymphoproliferative disorders such as chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma, hairy cell leukaemia, and multiple myeloma. Furthermore, evaluation of cytopenia, thrombocytosis, leukocytosis, anaemia, and iron status can also be done[1].

This is also an important tool in the diagnosis of non haematological disorders like storage diseases, granulomatous lesions, metastatic carcinoma, PUO, and disseminated infection in immunocompromised hosts[2].

The two most important techniques used for the diagnosis are bone marrow aspiration and bone marrow trephine biopsy which are complementary to each other. Aspiration of the marrow is primarily utilised for cytological assessment with analysis directed towards morphology and obtaining a differential cell count. Biopsy is essential for diagnosis in a dry tap or blood tap which occurs when the marrow is fibrotic or densely cellular. Only a biopsy allows a complete assessment of marrow architecture and pattern of distribution of any abnormal infiltrates[2].

In the present study, 460 consecutive indoor patients above the age of 18 years were evaluated for the clinical diagnosis by doing bone marrow aspiration and bone marrow trephine biopsy in a Medical College Hospital of Himachal Pradesh over a period of one year, and efficacy of bone marrow aspiration was compared with that of bone marrow examination. This is the first study of its kind from Himachal Pradesh.

Material and methods

A total of 460 bone marrow investigations were performed. Cases above 18 years of age were included in this study. The bone marrow samples were obtained from the posterior iliac spine. The aspiration needle was passed perpendicular into the cavity of the bone and 0.2 - 0.3 ml of marrow content was sucked with the help of a 20 ml syringe. Jamshedi needle was used for bone marrow biopsy. The specimen was fixed in 10% formalin and decalcified with EDTA overnight.

Giemsa staining was done for aspiration smears and haematoxylin-eosin (H-E) stain was used for biopsy.

Periodic Acid Schiff stain (PAS), myeloperoxidase (MPO), non specific esterase (NSE), Sudan black and Z-N stain were done whenever indicated.

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Results

A total of 460 cases were subjected to bone marrow aspiration and bone marrow biopsy. 359 (78%) examinations provided either the diagnosis or diagnostic clues to the disease process. 101 (22%) cases revealed a normal study. Of the 359 positive cases, 300 cases were of haematological disorders, while 59 were of non haematological disorders. Out of 300 haematological disorders, 179 (59.6%) were males and 121 (41.6%) were females. Out of 59 non haematological disorders, 37 (62.7%) were males and 22 (37.2%) were females.

Of the 460 bone marrow samples examined there were 153 cases of nutritional anaemia. Megaloblastic anaemia was the commonest anaemia diagnosed on bone marrow examination, accounting for 18.47% of all the bone marrow samples examined. 20 cases of hypoplastic anaemia were diagnosed on bone marrow aspiration, while 3 more cases were diagnosed on bone marrow biopsy examination.

Table I: Comparative evaluation of bone marrow aspiration and bone marrow biopsy diagnosis (n-460).

Disorders	Bone marrow aspiration	Bone marrow biopsy	Diagnostic accuracy of bone marrow aspiration (%)
Nutritional anaemia	153	147	–
Hypoplastic anaemia	20	23	86.9
Leukaemia	30	31	96.7
NHL-infiltration on bone marrow	54	61	88.5
Myeloproliferative disorder	01	06	16.6
Myelodysplastic syndrome	05	05	100
Multiple myeloma	20	20	100
Immune thrombo-cytopenic purpura	01	01	100
Granulomatous lesion	08	11	72.7
Metastasis	01	03	33.3
Leishmaniasis	04	04	100
Reactive bone marrow picture	40	41	97.5
Normal	100	101	99
Dry tap	23 (5%)	–	–
Inadequate	–	6 (1.3%)	–
Total	**460**	**460**	

Dry tap - 23
Inadequate on the biopsy – 06

Nutritional anaemia was diagnosed in 153 cases on aspiration, and only 147 cases were diagnosed on biopsy. Bone marrow aspiration appears to be a valuable diagnostic tool in nutritional anaemia.

Bone marrow aspiration diagnosed most of the cases of leukaemia 30/31 (96.7%), NHL infiltration 54/61 (88.5%), Myelodysplastic syndrome 5/5 (100%), multiple myeloma 20/20 (100%), ITP 1/1 (100%), leishmaniasis 4/4 (100%), reactive bone marrow picture 40/41 (97.5%), and granulomatous lesions 8/11 (72.7%). Two out of three cases of granulomatous lesions had revealed only reactive changes, while one case was diagnosed as megaloblastic anaemia on aspiration. Bone marrow biopsy provided diagnosis in additional one case of leukaemia, 7 cases of NHL infiltration, 5 cases of myeloproliferative disorders, 3 cases of granulomatous lesions, and 2 cases of metastatic lesions. These cases of metastatic lesions had revealed normal study on bone marrow aspiration. Dry tap was found in 23 cases (5%) of aspiration and inadequate material was seen in 6 cases of biopsy (Table I).

Out of 23 cases of dry tap, biopsy provided the diagnostic clue in 20 cases (Table II). 2 cases of normal study were diagnosed on bone marrow biopsy in which aspiration had given a dry tap or a diluted aspiration. In one case of dry tap, the biopsy section revealed only necrosis and fibrosis.

Table II: BMTB diagnosed cases in dry taps on BMA (n-23).

S. No.	Cases	Biopsy diagnosis	% of cases
1	Leukaemia	1	4.3%
2	Myeloproliferative disorder	5	21.7%
3	NHL infiltration in bone marrow	6	26%
4	Hypoplastic anaemia	3	13%
5	Anaemia	2	8.6%
6	Non specific reactive changes	3	13%
7	Normal study	2	8.6%
8	Inadequate	1	4.3%
	Total	**23**	**100%**

Discussion

Bone marrow examination is an important investigation carried out in the routine practice for the diagnosis of various haematological and non haematological disorders.

The commonest haematological disorder in the present study was anaemia with 173 cases (37.6%) belonging to this subset. Megaloblastic anaemia was the commonest

anaemia diagnosed on bone marrow examination (18.47%).

In the present study, 87% cases of hypoplastic anaemia were diagnosed on bone marrow aspiration while only additional 13% were diagnosed on bone marrow biopsy. Nanda *et al*[3] had similar findings in their study.

Out of the 153 cases of nutritional anaemia diagnosed on bone marrow aspiration only, 147 cases were confirmed on biopsy. It is a well known fact that aspiration is better in making out individual cell morphology whereas biopsy is useful in study of bone marrow architectural pattern and distribution[4]. This could be the reason that early megaloblastic change seen in an occasional erythroid cell was picked on aspiration and not biopsy.

In our study, there were 10 cases of non-Hodgkin's lymphoma infiltration which were diagnosed on bone marrow biopsy and were negative on bone marrow aspiration. 6 out of these 10 cases revealed a packed marrow pattern on bone marrow biopsy and had given a dry tap on aspiration. 4 out of 10 cases could have been negative on bone marrow aspiration due to focal involvement of bone marrow by NHL cells[5]. 3 cases of NHL were diagnosed on bone marrow aspiration which were negative on trephine biopsy (4.6%). This is in variance with the results of Musoloni *et al*[6] where 9.8 % cases were positive on only aspiration. This stresses the point that both aspiration and biopsy should be done in case of suspected NHL.

Out of 6 cases of myeloproliferative disorders, 5 cases (83.33%) were diagnosed on bone marrow biopsy where aspiration yielded a dry tap. This is in contrast with the findings of Sitalakshmi *et al* where only 18.75% cases revealed a dry tap[7]. The cause of the increased number of dry taps in myeloproliferative disorders could be due to the increased cellularity or increased fibrosis in the bone marrow[8]. In our study, 28% of granulomatous lesions were diagnosed on biopsy only whereas Nanda *et al* and Toi *et al* could diagnose 40% and 80% cases respectively on only biopsy as aspiration was inconclusive[3, 9]. As compared to the rest of the studies mentioned above, the number of cases diagnosed on only bone marrow biopsy in our study was less. A bilateral trephine biopsy could be the reason of a higher diagnostic yield in other studies[10]. In our study, two out of three cases (66.7%) of metastatic tumours were diagnosed on biopsy. Our findings are almost similar to those of Nanda *et al*, Toi *et al* and Chandra *et al*[3,9,11]. The greater diagnostic ability of bone marrow biopsy could be due to the focal involvement of the bone marrow and increased fibrosis associated with metastasis[10].

In the present study, bone marrow aspiration findings co-related well with the bone marrow biopsy findings in 432 (94%) cases. Of the rest 28 cases, 23 revealed a dry tap and 5 provided incomplete information on aspiration. The bone marrow biopsy gave the diagnosis of granulomatous and metastatic lesions in these 5 cases.

The diagnosis of leukaemia, myeloproliferative disorders, NHL and hypoplastic anaemia was made by biopsy in cases of dry tap. The incidence of dry tap in our study was less than other studies[12, 13]. Bone marrow biopsy proved to be of same diagnostic value in these studies as our study.

To conclude, it is the clinician's decision whether to do bone marrow aspiration alone or combine it with bone marrow biopsy depending upon the clinical situation. Both are complementary to each other as has been brought out in this study. Bone marrow biopsy is particularly required for the diagnosis of NHL infiltration, myeloproliferative disorders, aplastic/hypoplastic anaemia, metastatic tumours and granulomatous lesions.

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ORIGINAL ARTICLE

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Study on the role of urinary inhibitors of *in vitro* ion precipitation in the aetiopathogenesis of renal calculosis

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Abstract

***Background:** Renal calculosis is a multifactorial problem which initiates with the formation of micro-crystals in urine and terminates with the formation of a mature calculus in the kidneys. Out of many intrinsic and extrinsic factors postulated to be involved in the aetiology of renal calculosis, various inhibitors present in urine and other body fluids have been thought to be primarily responsible for the formation of calculi.*

***Methods:** Using an in vitro assay system of mineralisation, the level of the inhibitors in the urine of 30 normal persons and 98 kidney stone patients was determined and expressed in term of inhibitory units.*

***Results:** The level of the inhibitors was found to be significantly higher ($P < 0.0001$) in normal females as compared to normal males and in both sexes of normal persons as compared to kidney stones patients of identical sex. The studies further revealed that the chemical nature of the inhibitors differs between normal persons and kidney stone patients. The urine of a normal person is much more potent to inhibit calcium and phosphate precipitation than kidney stone patients of identical sex ($p > 0.001$). In contrast to normal persons, in kidney stone patients the ability to act by preferentially binding to calcium is absent and this difference may be the key molecular event to turn a normal person into a stone former. Although an inverse relationship was found to exist between the size of the stones and the level of the urinary inhibitors in the male kidney stone patients, no relationship was found in female kidney stone patients.*

***Conclusion:** The concentrations and activities of urinary inhibitors play an important role in the aetiopathogenesis of renal calculosis. In addition to the urinary inhibitors, sex hormones appear to be involved in controlling the size of the renal stones.*

***Key words:** Kidney, calculosis, calcium oxalate, calcium phosphate, inhibitors.*

Introduction

Urinary stone disease has afflicted humans since antiquity. Urinary stones have been shown to widely vary in size, shape, colour, composition, and texture. Approximately 80% of the urinary stones have been shown to be composed of calcium salts – calcium oxalate being the most predominant constituent as compared to calcium phosphate. The remaining 20% of the urinary stones are composed of uric acid, carbonate, cystine, et cetera[1]. Urolithiasis is a clinical disorder which is caused by multiple aetiological factors which could be pre-urinary and/or urinary. The pre-urinary factors can either be intrinsic or extrinsic. The extrinsic factors include geographical distribution, climate, water intake, and dietary habits. The intrinsic factors are age, sex, occupation, and ethnic/racial/familial background[2-3].

The precipitation of inorganic ions as solid mineral phase (calculus) clearly depends upon the saturation state of the media or body fluids with respect to mineral phase constituents and/or the concentration of the bio-molecules which by forming soluble complexes with the reactive ions can keep these in soluble phase. Since human urine and other body fluids are known to be super saturated with respect to calcium oxalate and calcium phosphate, the question that naturally arises is, why healthy people can produce crystaluria without causing calculosis? One way to explain the above apparent disparity could be by postulating that urine of normal persons contains biomolecules which by acting as potent inhibitors of mineralisation are involved in preventing calculosis. The potent inhibitory biomolecules may either be absent or present in lower concentrations in the urine of kidney stone patients[4].

From time to time, based upon *in vitro* and *in vivo* studies, human urine has been shown to contain various cations, anions, and other micro-or macro-biomolecules which by either acting as inhibitors or promoters of mineralisation may be involved in the control of urolithiasis[5].

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Based upon their ability to inhibit mineralisation of the rachitic rat cartilage, urine from normal persons and kidney stone patients was classified as good and evil urine respectively[6]. Male human beings have further been shown to be much more prone to urinary stone disease as compared to their female counterparts[7-8].

If the urinary inhibitors indeed play an important role in the aetiology of urolithiasis, it was essential to first quantize and then compare the level of the inhibitory molecules in the urine samples obtained from the following:

i) Normal male and female persons.

ii) Normal human beings and kidney stones patients of identical sex.

Establishing a possible correlation between the levels of the urinary inhibitors present in the urine samples obtained from the kidney stone patients with the size of the stone(s) present in the respective patient will provide additional evidence regarding the physiological significance of the urinary inhibitors in the aetiology of urolithiasis. Review of literature revealed that no studies had been conducted to investigate the above three aspects, hence, these formed the objectives of the present study.

Materials and methods

The study was conducted in the department of Biochemistry, Himalayan Institute of Medical Sciences, Swami Rama Nagar, Jolly Grant, Dehradun, Uttarakhand, over a period of 12 months. During this period, the samples were collected from 30 normal persons and 98 kidney stone patients, who either visited the urology OPD or were admitted in the urology ward for surgical interventions with the following inclusion and exclusion criteria.

Inclusion criteria: Male and female subjects (normal persons and kidney stone patients) above 21 years of age. Normal persons were those volunteers having no history of previously suffering from any disease related to mineral metabolism. Urolithiatic patients had no other abnormality except urolithiasis.

Exclusion criteria: Male and female subjects (normal persons and kidney stone patients) less than 21 years of age, patients of acute/chronic kidney failure and patients having any other abnormality other than urolithiasis.

A detailed record of history, including personal, past, family history, symptoms related to urolithiasis and general examination was maintained for each normal person and kidney stone patient. *In vitro* mineralisation studies were conducted by employing homogeneous systems of mineralisation.

Homogeneous system of mineralisation

For the homogenous system of mineral phase formation, modified method of Singla and Jethi was employed not only to study initial mineral phase formation but also the effect of various test samples on this process[9]. The standard incubation system employed to study the extent of calcium and phosphate precipitation as mineral phase is given in Table I. Different amounts of the stock solutions of different reagents were used to give the final concentration as specifically indicated. The pH of all the reagents was adjusted to 7.4 before addition to the reaction system. NaCl was used to keep the ionic strength of the medium relatively constant during the reaction. Urine samples were added to the reaction system after adjusting their pH to 7.4. Final volume of each assay system was adjusted to 5 ml with the addition of glass distilled water. The concentrations of calcium and phosphate ions in the various urine samples used were determined and properly compensated for in the test assay systems so as to ensure that both the control and the test assay systems contained the same concentration of these ions at the start of the experiment. The reaction was conducted in the test tubes at 37°C for 15 min. All the reagents except phosphate were added together initially and phosphate was used to start the reaction. After incubation, the tubes were centrifuged at approximately 5,000 rpm for 10 min to obtain the precipitates. Each precipitate was dissolved in 0.1N HCl to give the final volume of 5 ml. The concentrations of calcium and phosphate in different samples thus obtained were determined by the micro-analytical method of Baginski *et al* and Amador and Urbani respectively[10-11]. The concentration of the ions in the precipitates represented the extent of mineral phase formation.

Test samples

Approximately 5 - 20 ml of fresh urine samples from 15 normal male persons, 15 normal female persons and 98 kidney stone patients (68 male and 30 female) were collected and stored at 4°C without the addition of any preservative. Out of 68 male kidney stone patients, 14 had bilateral and 8 had staghorn stones. Out of 30 female kidney stone patients, 8 had bilateral and 3 had staghorn stones. Record of the size of stone(s) in each kidney stone patient was maintained to find a possible relationship between the level of inhibitors in the urine and the size of their stones.

Results

For the present studies, *in vitro* system of mineralisation was used to investigate the following:-

i) Standardisation of the *in vitro* mineralisation system to study the ability of test samples to influence mineralisation.

ii) The ability of urine samples obtained from male and female normal persons and kidney stone patients to influence mineralisation. The assay was conducted within 24-hour of sample collection.

iii) To develop a suitable unit for measuring the inhibitory potencies of various urine samples and to compare the inhibitory potencies of urine samples obtained from the normal persons with urolithiatic patients of the identical sex in terms of inhibitory units.

iv) To establish a possible correlation between the size of stones and the inhibitory potencies of the urine samples obtained from the respective urolithiatic patients.

Table I: Homogeneous system of *in vitro* calcium and phosphate precipitation.

S. No	Reactants	Stock solutions concentrations (mM)	Volume of stock solutions added to the reaction system (ml)	Final conc. in the reaction system (mM)
1.	$CaCl_2$	50.0	0.5	5.0
2.	Tris-HCl Buffer (pH 7.4)*	87.5	1.0	17.5
3.	NaCl*	525.0	1.0	105.0
4.	Glass distilled water ± urine sample	–	2.0	As specifically calculated
5.	KH_2PO_4	50.0	0.5	5.0

** Both can be added together in one solution.*

Standardisation of *in vitro* mineralisation assay system

For the homogeneous *in vitro* assay system, given in Table I, super-saturated solution of Ca^{2+} and HPO_4^{2-} ions having Ca^{2+} X HPO_4^{2-} product > $6X10^{-6}$ M^2 (the solubility product of $CaHPO_4$) at pH 7.4, was employed. The results presented in Table II, demonstrate that when 25 µmoles each of Ca^{2+} and HPO_4^{2-} ions were added to the reaction system, 15.00 ± 0.44 µmoles of Ca^{2+} and 9.00 ± 0.36 µmoles of HPO_4^{2-} got precipitated-out as mineral phase. The ratio of Ca^{2+}/ HPO_4^{2-} ions in the mineral phase thus formed comes out to be 1.66:1. By adding the ions recovered from the supernatants to the ions present in the precipitates, it is apparent that 98.4% of the added Ca^{2+} and 99.0% of the added HPO_4^{2-} can be accounted for.

Table II: Initial precipitation of Ca^{2+} and HPO_4^{2-} ions as mineral phase using homogeneous system of *in vitro* mineralisation

S. No.	Particulars	Ca^{2+} (µ moles)	HPO_4^{2-} (µ moles)
1.	Ions initially added in the reaction system	25.0	25.0
2.	Ions recovered from the precipitates at the end of incubation	15.00 ± 0.44	9.00 ± 0.36
3.	Ions recovered from the supernatants	9.60 ± 0.28	15.75 ± 0.35

All values are Mean ± SD of 15 replicates.

Ability of urine samples obtained from normal persons and kidney stone patients to influence *in vitro* mineralisation (calcium and phosphate precipitation)

The effect of urine samples from normal persons on *in vitro* mineralisation: Results presented in Table III demonstrate that the urine samples obtained from the normal male and female persons have the ability to inhibit the precipitation of Ca^{2+} and HPO_4^{2-} ions as mineral phase. On an average, 0.5ml of urine samples obtained from the normal male and female persons were found to inhibit the mineralisation as measured by the precipitation of Ca^{2+} and HPO_4^{2-} ions by 42 and 79% (average of precipitation of Ca^{2+} and HPO_4^{2-}) respectively.

The above studies further demonstrate that an almost linear relationship exists between the amount of the urine samples used and the per cent inhibition of the precipitation of both calcium and phosphate ions as mineral phase. Based upon the above facts, one can very easily define the inhibitory potencies in term of inhibitory units. One inhibitory unit being the amount of urine which can inhibit the precipitation of either Ca^{2+}or HPO_4^{2-} ions by 50%. Applying the above definition, the inhibitory ability of urine samples obtained from both the normal and kidney stones male/female subjects were expressed in terms of inhibitory units. The studies revealed that based upon the precipitation of calcium or phosphate ions as mineral phase, normal male and female persons were found to excrete 181.1 ± 25.0 or 165.8 ± 27.3 and 356.9 ± 32.5 or 300.1 ± 30.3 Inhibitory Units/100ml of urine respectively. The differences between the sexes were found to be highly significant at $P < 0.0001$. At all the concentrations of urine samples used, in both the sexes of normal persons, much higher percentage inhibition of calcium as compared to that of phosphate was obtained.

The effect of urine samples from kidney stone patients on *in vitro* mineralisation: Results presented in Table IV clearly indicate that like normal persons, urine samples obtained from the kidney stone patients were also found to be capable of inhibiting the precipitation of calcium

Table III: Effect of urine samples from normal persons on *in vitro* mineralisation (calcium and phosphate precipitation).

S. No.	Urine used (ml)	Per cent inhibition of ion precipitation			
		Normal male persons		Normal female persons	
		Calcium	Phosphate	Calcium	Phosphate
1	0.1	09.26 ± 1.79	08.46 ± 1.76	18.40 ± 2.43	16.00 ± 2.59
2	0.2	18.06 ± 2.37	15.40 ± 3.48	34.06 ± 5.44	30.66 ± 4.45
3	0.3	26.93 ± 3.18	24.20 ± 2.65	53.53 ± 7.87	44.93 ± 4.04
4	0.4	34.93 ± 6.05	32.33 ± 5.53	75.06 ± 2.46	58.80 ± 7.37
5	0.5	45.26 ± 4.25	40.46 ± 3.82	87.33 ± 3.77	70.86 ± 6.39

• *All the values are Mean ± SD of 15 subjects.*

and phosphate ions as mineral phase. At all the concentrations of the urine samples used, urine samples obtained from both the normal male and female persons were found to be much more potent to inhibit mineralisation as compared to those obtained from the kidney stone patients of the identical sex. These differences were found to be highly significant at $P < 0.0001$.

The inhibitory ability of urine samples obtained from the kidney stones patients were further expressed in terms of inhibitory units and the results thus obtained showed that on an average based upon the precipitation of calcium or phosphate ions as mineral phase, kidney stones male and female patients were found to excrete 119.4 ± 22.9 or 114.1 ± 23.3 and 202.9 ± 24.9 or 201.4 ± 27.2 Inhibitory Units/ 100ml of urine respectively. These differences between the normal persons and kidney stone patients in both the sexes were found to be highly significant at $P < 0.0001$. In contrast to normal persons, no significant differences were observed in the kidney stone patients when the ability of their urine samples to influence the precipitation of calcium and phosphate ions as mineral phase were compared. In normal patients the differences were found to be highly significant, however, in kidney stone patients the differences were not significant at $P < 0.05$.

Relationship between the size of the stones and inhibitory potencies of urine samples obtained from kidney stone patients

The present studies strongly suggested that urinary inhibitory biomolecules play an important role in the control of renal calculosis. In the male kidney stone patients, as expected, an inverse relationship was found to exist between the size of the stones and inhibitory potencies of their urine samples (Fig. 1a and 1b). In female kidney stone patients, in contrast to male kidney stone patients, at any constant value of the inhibitory potency of the urine samples, a very significant variation in stone sizes (ranging from 5 to 40 mm) was present (Fig. 2a and 2b). It is thus apparent that in female kidney stone patients no relationship, whatsoever, exists between the urinary inhibitory potencies and the size of the stones (not significant at $P < 0.05$).

Discussion

Standardisation of *in vitro* mineralisation assay system: The conventional methods used to determine and quantize the inhibitory potencies of various samples employ the formation of mineral phase either in the presence or absence of a foreign matter, i.e., heterogeneous or homogenous precipitation respectively[4,12-17]. Both these assay systems have some advantages and disadvantages. Methods employed by various workers to study the precipitations of Ca and P/Ox ions as CaP/CaOx mineral phase respectively, either involve the use of sophisticated equipments in heterogenous precipitation[15-16] or the formation of precipitates on solid supports during homogenous precipitation, requires repeated transfers[17-18]. All the above methods used are not only time consuming but also error prone.

For the present investigations, a simple and quick method employing homogeneous system of *in vitro* mineralisation was used to study not only the extent of mineral phase formation as measured by the precipitation of calcium and phosphate ions (under physiological conditions of temperature, pH and ionic strength), but also the effect of various test samples on this process.

The results presented in Table II demonstrate that almost 100% recovery of the added ions can be made from the precipitates and the supernatants. Although no direct attempt was made to determine the nature of the mineral phase formed during the course of the present studies by using various biophysical methods, yet the indirect

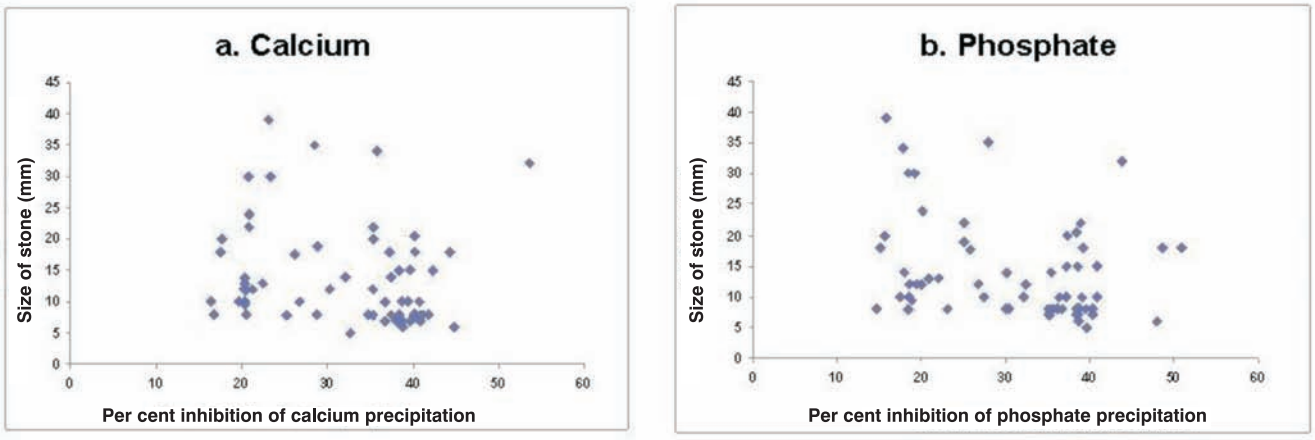

Fig. 1: *Relationship between stone size and per cent inhibition of ion precipation by urine samples from male kidney stone patients.*

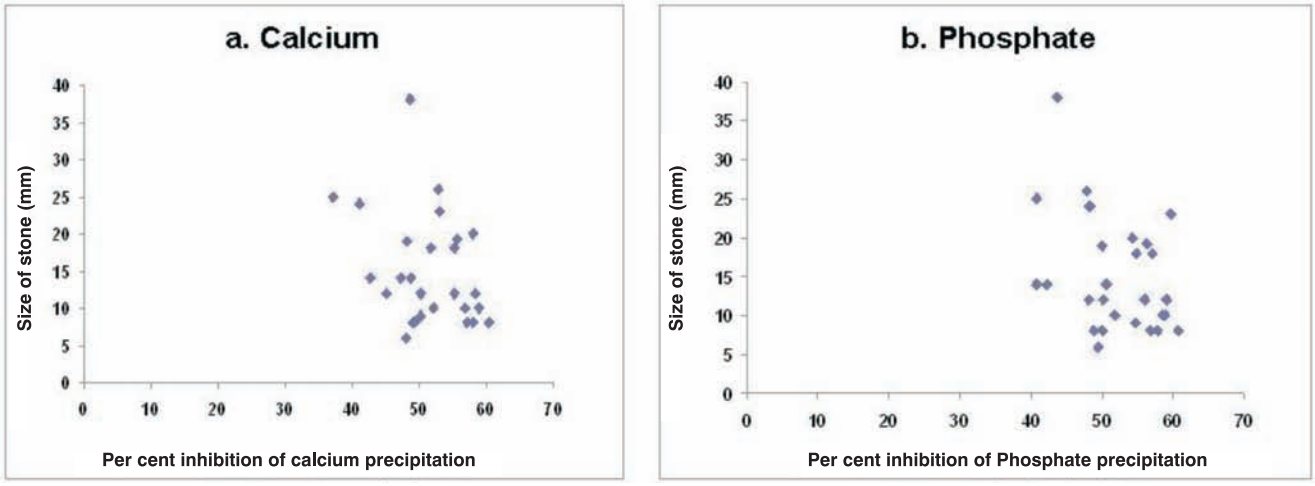

Fig. 2: *Relationship between stone size and per cent inhibition of ion precipation by urine samples from female kidney stone patients.*

evidence tends to suggest that the chemical nature of the mineral phase formed resembles hydroxyapatite (OHAP) which has Ca^{2+}/HPO_4^{2-} ions ratio of 1.67:1.

Effect of urine samples from normal persons and kidney stone patients on *in vitro* mineralisation (calcium and phosphate precipitation): Results obtained during the present studies clearly demonstrate that human beings excrete various biomolecules in their urine which act as potent inhibitors of mineral phase formation. It is apparent from the data obtained during the present studies (Table III) that as compared to the normal male persons, urine samples obtained from the normal female persons are approximately twice as potent to inhibit the precipitation of calcium and phosphate ions as mineral phase. The above findings provide experimental evidence to the observations of various scientists that males are 2 - 3 times more prone to the renal stone disease as compared to the females of the identical age group[19-20]. Analysis of variance showed that the differences between sexes were highly significant at $P < 0.0001$. It is interesting to note that during the approximately one-year period of the present study, as per our selection criteria using the identical inclusion and exclusion criteria, 68 male and 30 female patients got themselves selected for the studies. The above observation is in conformity with the experimental findings made during the present studies and the observations of other workers that the incidence of kidney stones is much higher in males as compared to the females of the identical age group.

Although during the present studies no attempt was made to isolate and purify the potent inhibitory biomolecules responsible for the inhibitory potencies of the urine samples obtained from the normal male and female persons, yet it is safe to conclude that the main inhibitory biomolecules are acidic in nature and are negatively charged under the present experimental conditions. The above conclusion is based upon the observation that at all concentrations, urine samples obtained from both the normal male and female persons

were found to be much more potent to inhibit the precipitation of calcium ions as compared to that of phosphate ions. The difference between ions were found to be significant at $P < 0.001$.

The studies (Table IV) suggest that in both sexes as compared to kidney stone patients, the urine samples obtained from the normal persons were found to be much more potent ($P < 0.0001$). The above observation is not only in conformity with the definition of "good" and "evil" urine proposed by Howard and Thomas[14], but also strongly suggests that inhibitors may play an important role in the aetiopathogenesis of renal calculosis.

It is logical to presume that the critical factor which determines whether a given person will form a stone or not is not the concentration of the stone forming constituents in the urine but the concentration or activities of the urinary inhibitors. The above hypothesis can perhaps also explain why only some persons in a family form renal stones when everybody almost consumes the same diet.

Lower inhibitory potencies of the various samples observed during the present studies could either be due to the lower concentrations of the potent inhibitory biomolecules in these samples or it could be due to the presence of these inhibitory biomolecules in their relatively inactive forms in the said samples. The results obtained during the present studies do provide indirect evidence which tends to suggest that the chemical nature of the potent inhibitory biomolecules differ between normal persons and kidney stone patients. The above conclusion is based upon the fact that the inhibitory biomolecules present in the urine of normal male and female subjects were found to inhibit *in vitro* mineralisation by preferentially binding to the calcium ions. This ability of the urinary biomolecules to act by preferentially binding to calcium ions was completely abolished in the case of kidney stone patients. An inhibitory biomolecule when phosphorylated becomes active (negatively charged) and it inhibits mineral phase formation by preferentially binding to the calcium ions. Upon dephosphorylation it becomes relatively inactive by losing its negative charge and hence the ability to act by preferentially binding to the calcium ions. Interestingly review of literature revealed that phosphatase activity has been known to increase in bones during active mineral phase formation[21-23] and phosphorylated biomolecules (fructose 1-6 bis phosphate, & nucleoside di & tri phosphates) lose their ability to inhibit *in vitro* mineralisation upon dephosphorylation[24-26]. These studies provide additional support to the above proposed hypothesis.

Relationship between renal stones and the inhibitory potencies of the urine samples obtained from kidney stone patients: The present study (Fig. 1a and b) clearly demonstrates, as expected, that an inverse relationship exists between the size of the stones and the inhibitory potencies of the urine samples obtained from the male kidney stone patients. However, no such relationship was found to exist in case of female kidney stone patients. These results could be interpreted to mean that in addition to the urinary inhibitors, sex hormones may also play an important role in the aetiology of renal calculosis.

The observations made during the present study assume practical significance in the control/ management of the renal calculosis problem. It is logical to presume that irrespective of the nature of the chemical change at the

Table IV: Effect of urine samples from normal persons and kidney stone patients on *in vitro* mineralisation (calcium and phosphate precipitation).

S. No./ Sex	Urine used (ml)	Per cent inhibition of ion precipitation			
		Normal persons		Kidney stone patients	
		Calcium	Phosphate	Calcium	Phosphate
Male					
1	0.30	26.93 ± 3.18***	24.20 ± 2.69***	16.22 ± 2.47***	16.59 ± 3.01***
2	0.50	45.26 ± 4.25***	41.46 ± 3.82***	32.35 ± 3.24***	31.04 ± 4.05***
Female					
3	0.30	53.33 ± 5.87***	44.93 ± 4.04***	28.64 ± 3.49***	28.31 ± 3.78***
4	0.50	87.33 ± 3.77***	70.86 ± 6.09***	51.72 ± 4.21***	51.15 ± 4.81***

The above values are Mean ± SD 15 male and 15 female normal persons and 68 male and 30 female kidney stone patients.
** P < 0.05; * P < 0.001; * P < 0.0001*

molecular level which can turn a normal person into a stone former, this change must occur well in advance of the clinical manifestation of urolithiasis. Screening human population for potential stone formers, at least in the high risk stone belt areas, will go a long way in helping the clinicians to take various prophylactic measures to prevent/delay the formation of the stones in the urinary tract.

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"God give us deliverance from
Not letting the well alone,
Treating human beings as cases,
And making the treatment of the disease more difficult
than the disease itself."

– Sir Robert Hutchison (1871-1960)

REVIEW ARTICLE

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Role of aspirin in the primary prevention of atherosclerotic vascular disease: A reappraisal

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Abstract

Aspirin has been used conventionally in the secondary prevention of cardiovascular events for decades. However, the role of aspirin in primary prevention remained unclear. Various randomised-controlled trials have indicated that low-dose aspirin is associated with a reduction in cardiovascular events, despite the fact that aspirin increases the risk of haemorrhagic stroke and gastrointestinal bleeding even at low dosage. The risk-to-benefit ratio of aspirin remains unclear. Aspirin has a variable effect in men and women. The dose of aspirin used by clinicians worldwide is arbitrary and not based on the results of randomised-controlled trials. Reliable data on primary prevention with aspirin for diabetic patients is lacking and requires further trials.

Key words: Aspirin, diabetes, atherosclerotic disease, myocardial infarction, stroke, primary prevention.

Introduction

The spectrum of atherosclerotic diseases includes coronary heart disease (CHD), cerebrovascular and peripheral arterial diseases. There are various therapies for managing atherosclerotic disease, which include medical treatment, percutaneous intervention, and surgery. However, antiplatelet therapy remains the mainstay of treatment[1].

Aspirin (acetylsalicylic acid) was introduced in 1899. It irreversibly inactivates cyclo-oxygenase and prevents formation of both thromboxane A_2 and prostacyclin. Low-dose aspirin in the dose of 75-150 mg/day orally reduces the synthesis of thromboxane A_2 thereby exerting antithrombotic effects without significant impairment of prostacyclin synthesis[2].

Aspirin has been used for secondary prevention of atherosclerotic disease for more than five decades. High-risk patients derive benefit from long-term antiplatelet therapy, which reduces the risk of serious vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death) by about 10 - 20 per 1,000 per year[3]. However, this benefit comes at the price of an increase in serious bleeding episodes[1,3].

Current guidelines recommend that aspirin should be used widely for primary prevention in populations at increased risk of coronary heart disease[3,4]. It has been suggested that since age is a major risk factor for coronary heart disease, all people above a specific age should be prescribed low-dose aspirin[3].

Primary prevention can be deferred until there is some evidence of occlusive vascular disease in view of the fact that it could avoid the increased risk of bleeding. However, the main disadvantage of deferral is that the first manifestation of disease might be fatal.

In this article we review the effectiveness and harms of aspirin therapy in primary prevention of atherosclerotic vascular disease.

Assessment of risk for cardiovascular disease

The net beneficial effect of aspirin depends on the initial risk of coronary heart disease events and for gastrointestinal bleeding. Accurate assessment of an individual's cardiovascular risk should be done before considering the use of aspirin for primary prevention. A tool for predicting coronary heart disease events was developed on the basis of the Framingham Heart Study data. This tool uses sex, age, smoking, diabetes, blood pressure and cholesterol levels as risk factors for coronary heart disease[5]. The calculator is available online at http://healthlink.mcw.edu/article/923521437.html. A tool to calculate the risk of stroke was also developed on the basis of the Framingham data, which uses hypertension, age, sex, diabetes, smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy as major risk factors[6]. The stroke risk calculator is available online at www.westernstroke.org/PersonalStrokeRisk1.xls.

Trials of primary prevention with aspirin

There have been six major primary prevention trials of

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aspirin – British Medical Doctors (BMD)[7], Physicians' Health Study (PHS)[8], Thrombosis Prevention Trial (TPT)[9], Hypertension Optimal Treatment (HOT)[10], Primary Prevention Project (PPP)[11], and Women's Health Study (WHS)[12]. These trials did not focus specifically on diabetic patients. Women were not included in BMD, PHS, and TPT trials. WHS focussed solely on women, whereas the proportion of women in HOT and PPP was 47% and 57%, respectively. Aspirin was used in the lowest dose of 100 mg every alternate day in WHS trial. Other trials used aspirin in the dose of 75 to 500 mg per day. Participants at increased risk of gastrointestinal bleeding based on a history of peptic ulcer disease were excluded in these trials. Apart from PPP, none of the other trials used lipid-lowering therapy.

The British Medical Doctors (1988) trial was conducted to see the effects of 500 mg of daily aspirin on the incidence of, and mortality from myocardial infarction, stroke or any other vascular events[7]. The group receiving aspirin had a 10% lower mortality as compared with the control group. However, this difference was not statistically significant. An interesting observation was that physically disabling strokes were common in the group to which aspirin was prescribed.

The Physicians' Health Study (1989) was conducted to determine the effects of low-dose aspirin (325 mg every alternate day) on cardiovascular mortality and whether beta-carotene reduces the incidence of cancer[8]. The risk of myocardial infarction was reduced by 44% (relative risk, 0.56; 95% CI 0.45-0.70; $p < 0.001$) in the aspirin group (254.8 per 1,00,000 per year as compared with 439.7 per 1,00,000 per year in the placebo group). A stastically insignificant increase in the risk of stroke was observed in the aspirin group. Mortality from all cardiovascular causes was not reduced in the aspirin group (relative risk, 0.96; 95% CI 0.60-1.54). The benefit of reduction of myocardial infarction was apparent only in those above 50 years of age. Mortality benefit was observed at all levels of cholesterol. The relative risk for peptic ulcer in the aspirin group was 1.22 (95% CI 0.98-1.53; $p = 0.08$).

The Thrombosis Prevention Trial (1998) evaluated low intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease (IHD)[9]. The incidence of IHD was reduced by 20% (95% CI 1%-35%, $p = 0.04$) in the aspirin group. This effect was observed due to a 32% reduction (95% CI 12%-48%, $p = 0.004$) in non-fatal events. All IHD events were reduced by 2.6 and 2.3 per 1,000 person years in the warfarin and aspirin groups, respectively. All IHD events were reduced by 34% (95% CI 11%-51%, $p = 0.006$) in the combined warfarin and aspirin group. This combination was associated with an increased risk of haemorrhagic and fatal strokes. The outcome of TPT trial was that aspirin reduces non-fatal IHD and warfarin reduces all IHD mainly because of an effect on fatal events. The combination of warfarin and aspirin was more effective in the reduction of IHD than either agent alone.

The Hypertension Optimal Treatment trial (1998) evaluated the benefit of low dose aspirin in the management of essential hypertension and also assessed the optimum target diastolic blood pressure[10]. Major cardiovascular events were reduced by 15% ($p=0.03$) and myocardial infarction by 36% ($p=0.002$) in the aspirin group. There was no effect on stroke events. Seven fatal bleeds were observed in the aspirin group ($n = 9399$) and eight in the placebo group ($n = 9391$). There were 129 non-fatal bleeds in the aspirin group and 70 non-fatal bleeds in the placebo group ($p<0.001$).

The Primary Prevention Project (2001) evaluated the effects of low-dose aspirin (100 mg/day) and vitamin E (300 mg/day) in the prevention of cardiovascular events in patients with one or more cardiovascular risk factors[11]. There was a non-significant reduction in the primary endpoint and in total cardiovascular events in the aspirin treated subgroup versus non-diabetic subgroup [RR 0.90 vs 0.59 and RR 0.89 vs 0.69, respectively]. A stastically insignificant increase in total cardiovascular mortality was observed in the aspirin treated diabetic subgroup versus the non-diabetic subgroup [RR 1.23 vs 0.32].

In 2002, a systematic overview of the aforementioned five primary prevention trials of aspirin was done by the United States Preventive Services Task Force (USPSTF)[13, 14]. Overall, the risk of combined non-fatal and fatal CHD events was significantly reduced in the aspirin group (absolute risk reduction 0.5%) which represents a proportional CHD risk reduction of 28% (odds ratio [OR], 0.72; 95% CI 0.60-0.87). However, the risk of major gastrointestinal bleeding (OR, 1.7; 95% CI 1.4-2.1) and haemorrhagic stroke (OR, 1.4; 95% CI 0.9-2.0) was found to be increased with aspirin. There was no significant effect on total strokes and all cause mortality. The drawback of the US Preventive Services Task Force systematic overview was that it did not clarify whether gender, old age, diabetes mellitus or hypertension modify the effect of aspirin.

The Women's Health Study (2005) studied the effect of 100 mg of aspirin on alternate days or placebo in 39,876 healthy women 45 years of age or older and then followed them for 10 years for the first major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes)[12]. The aspirin group had 477 major cardiovascular events ($n = 19,934$) as compared with 522 in the placebo group ($n = 19,942$) during follow up. The risk reduction in the aspirin group was 9% (RR, 0.91; 95% CI 0.80-

0.03; p = 0.13), which was stastically insignificant. The aspirin group had a 17% reduction in the risk of stroke as compared with the placebo group (RR, 0.83; 95% CI 0.69-0.99; p = 0.04), mainly because of a 24% reduction in the risk of ischaemic stroke (RR 0.76; 95% CI 0.63 to 0.93; p=0.009). The increase in the risk of haemorrhagic stroke was also insignificant (relative risk 1.24; 95 % CI, 0.82 to 1.87; p=0.31). There was no significant effect on the risk of fatal or nonfatal myocardial infarction (RR 1.02; 95% CI 0.84-1.25; p=0.83) or death from cardiovascular causes (RR 0.95; 95% CI 0.74-1.22; p = 0.68) in the aspirin group as compared with placebo. Serious gastrointestinal bleeding was found to be more frequent in the aspirin group (RR 1.40; 95% CI 1.07-1.83; p = 0.02). WHS concluded that the risk of major cardiovascular events, ischaemic stroke, and myocardial infarction among women 65 years of age or older was reduced by aspirin therapy.

In view of these results, modified recommendations which specifically focused on gender based effects of aspirin were given by the US Preventive Services Task Force in 2009[15]. These recommendations are shown in Box 1.

Box 1: USPSTF 2009 recommendations for the use of aspirin in primary prevention of atherosclerotic vascular disease.

- Aspirin should be used for men aged 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to increased gastrointestinal bleeding. (Level A recommendation).
- Aspirin should be used for women aged 55-79 years when the potential benefit due to a reduction in ischaemic strokes outweighs the potential harm due to increased gastrointestinal bleeding. (Level A recommendation).
- Current evidence is insufficient to assess the balance of benefits and harms of aspirin for cardiovascular disease prevention in men and women 80 years or older (Level I recommendation).
- Aspirin can be used for stroke prevention in women younger than 55 years and for myocardial infarction prevention in men younger than 45 years. (Level D recommendation).

Level A: There is high certainty that the net benefit is substantial.

Level I: The current evidence is insufficient to assess the balance of the benefits and harms of the service.

Level D: There is high certainty that the service has no net benefits or that the harms outweigh the benefits.

Potential harms of primary prevention

Use of aspirin for the primary prevention of cardiovascular disease increases the risk of haemorrhage in both men and women[3, 12, 14, 15]. Gastrointestinal bleeding, peptic ulcers, haematuria, epistaxis, and easy bruising were more common in women prescribed aspirin therapy in the WHS trial. However, there was no statistically significantly increase in the risk of haemorrhagic stroke in the aspirin group (RR, 1.24 [CI, 0.82-1.87])[12].

Male sex, upper abdominal pain, and a past history of gastric ulcer were major risk factors for serious gastrointestinal bleeding with aspirin[15,16,17]. The use of NSAIDs with aspirin approximately triples or quadruples the rate of serious gastrointestinal bleeding[15]. Currently, lower doses or modified release aspirin is used worldwide in view of the risk of serious gastrointestinal bleeding. A meta-analysis of eight randomised controlled trials that used aspirin at doses of 50 to 162.5 mg/day in 49927 participants revealed that even low doses aspirin was associated with a significantly increased rate of gastrointestinal bleeding as compared with placebo. There was lack of evidence that dose reduction or the use of modified release formulations lower the risk of gastrointestinal bleeding[16]. A large Dutch trial in patients with transient ischaemic attacks revealed that aspirin was effective even at a dose of 30 mg/day[18].

Role of gender on the variable effects of aspirin in the prevention of cardiovascular events

Although it is widely accepted that aspirin reduces the risk of myocardial infarction on an average by 25%, considerable variation has been reported in trials[19,21]. The factors responsible for this variability are not clear. One important potential explanatory factor is gender. Women have an increased risk of aspirin resistance as compared to men, thus making aspirin less effective in women. Women have more severe atherosclerosis compared to age-matched men; have more co-morbid conditions and more extensive disease at the time of diagnosis[19].

Emerging data point towards major structural and physiological difference in coronary vasculature between men and women. Women have smaller and stiffer coronary vessels, as compared to men because of increased deposition of fibrotic tissue and remodelling of coronary vasculature. Atherosclerosis is more diffuse and extensive in women than in men[19,20].

A recent gender-specific meta-analysis using a Markov model revealed that the use of aspirin in men resulted in maximum decrease in the incidence of myocardial

infarctions (127 events per 100,000 person-years) and a comparatively smaller reduction in the incidence of ischaemic strokes in women (17 events per 100,000 person-years)[21]. Aspirin treatment in a hypothetical 55-year-old man with no additional cardiovascular risk factors resulted in slightly increased life expectancy and increased quality-adjusted-life-years (QALY). There was no similar benefit in women of a similar age group with no additional risk factors[21].

Meta-analysis of six randomised controlled trials which included > 50,000 women and 40,000 men revealed that the use of low dose aspirin in the primary prevention of cardiovascular events reduced the overall risk of cardiovascular events but increased the risk of bleeding (CNS and gastrointestinal) in both sexes[22]. Aspirin reduced the risk of myocardial infarction (but not stroke) in men and ischaemic stroke (but not myocardial infarction) in women[21].

Cardiovascular risk assessment and aspirin for primary prevention in diabetic patients

The general consensus among clinicians is that all patients with diabetes have a high risk of cardiovascular events. However, this fact does not hold true according to recent studies[23]. An important consideration is that diabetic patients may acquire additional risk factors over time, hence the treating clinicians should reassess their overall risk profile. The various risk assessment tools that can be used in patients with diabetes are enumerated in Box 2.

Box 2: Risk prediction tools in diabetes mellitus.

- UKPDS Risk Engine: http://www.dtu.ox.ac.uk/riskengine/index.php
- ARIC CHD Risk calculator: http://www.aricnews.net/riskcalc/html/RC1.html
- American Diabetes Association Risk Assessment Tool, Diabetes PHD: http://www.diabetes.org/phd

According to the Framingham study data, diabetes remains a strong risk factor for CHD (odds ratio for men and women, 1.5 and 1.8, respectively) and stroke (relative risk for men and women, 1.4 and 1.7, respectively)[1, 24]. However, there is a high risk for haemorrhagic stroke in diabetic patients according to the Honolulu Heart Program and the Framingham study[1].

Three trials – the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD)[24], the Early Treatment of Diabetic Retinopathy Study (ETDRS)[25], and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD)[26] – studied exclusive diabetic populations. JPAD and POPADAD trials studied mainly type 2 diabetic patients, whereas, ETDRS studied both type 1 and type 2 diabetic patients.

A meta-analysis of primary prevention trials that included the British Medical Doctors (BMD)[7], Physicians' Health Study (PHS)[8], Thrombosis Prevention Trial (TPT)[9], Hypertension Optimal Treatment (HOT)[10], Primary Prevention Project (PPP)[11], and Women's Health Study (WHS) [12] revealed that the use of aspirin in diabetic populations decreased the risk of total coronary heart disease, nonfatal myocardial infarction, and total cardiovascular events with a nonsignificant decrease in stroke risk, cardiovascular mortality, and all-cause mortality. However, this decrease in risk was stastically insignificant, as these trials did not focus specifically on the diabetic population.

The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial studied type 2 diabetic patients who were given low dose aspirin for the primary prevention of cardiovascular events[24]. The incidence of total atherosclerotic events (coronary, cerebrovascular and peripheral vascular events) in 2539 type 2 diabetic patients without previously documented cardiovascular disease, was not significantly different in the group that received prophylactic aspirin (81 or 100 mg once daily) than in the non aspirin group. None of the prespecified secondary end-points were reduced significantly in the low-dose aspirin group except fatal coronary and cerebrovascular events[24].

The ETDRS trial studied the effects of 650 mg of daily aspirin versus placebo among 3,711 patients with type 1 or type 2 diabetes between 18 to 70 years of age who had some degree of retinopathy. Both type 1 and type 2 diabetic patients on aspirin therapy experienced a decreased risk of non-fatal or fatal MI (RR 0.85, 95% CI 0.73-1.00). However, the incidence of stroke was higher in the aspirin group, although this difference was not statistically significant (RR 1.18, 99% CI 0.88-1.58). Men appeared to derive more benefit from aspirin therapy than did women for the prevention of MI (RR for men 0.74, 99% CI 0.54-1.00; RR for women 0.91, 99% CI 0.65-1.28), but this difference was also not statistically significant[25].

The POPADAD trial compared aspirin and/ or antioxidant therapy with placebo in reducing the incidence of cardiovascular events in 1276 adults above 40 years of age with diabetes and asymptomatic peripheral arterial disease. The primary end points were death from CHD or stroke, non-fatal MI or stroke, or amputation above the ankle for critical vascular ischaemia. Overall 18.2% primary events occurred in patients assigned to aspirin therapy versus 18.3% in those on placebo (hazard ratio 0.98, 95% CI 0.76-1.26) [26].

In a prospective Chinese study of 6,454 type 2 diabetic patients, low dose aspirin in primary prevention was associated with a paradoxical increase in cardiovascular disease risk. Surprisingly, aspirin did not confer any benefits in secondary prevention. In addition, the risk of GI bleeding with aspirin was high[27].

Patients with diabetes mellitus respond differently to the effects of aspirin. Diabetics may have a type of aspirin resistance, particularly to low doses. Various pathophysiological studies suggest that the platelets of diabetic patients are activated by different mechanisms. Persistent hyperglycaemia induces formation of endoperoxidases and thromboxane that counteract the action of cyclo-oxygenases that ultimately lead to thrombosis[24,28].

The American Diabetes Association (ADA) position statement on the standards of medical care in diabetes (2010) states that 75 to 162 mg/day of aspirin can be used for primary prevention in type 1 as well as type 2 diabetics at increased cardiovascular risk (10-year risk > 10%). This criteria will include most men > 50 years of age and most women > 60 years of age who have at least one additional major risk factor (family history of cardiovascular disease, hypertension, smoking, dyslipidaemia, or albuminuria). Aspirin for primary prevention in lower risk individuals, such as men < 50 years of age or women < 60 years of age without other major risk factors is not recommended because of lack of conclusive evidence[29].

There are two recent studies which will provide further information about the role of low-dose aspirin in the prevention of cardiovascular events specifically in patients with diabetes. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D)[30] is an ongoing Italian primary prevention trial comparing 100 mg/day aspirin to placebo in adults >50 years of age with type 2 diabetes mellitus who are also taking a lipid lowering drug simvastatin. Another trial, A Study of Cardiovascular Events in Diabetes (ASCEND)[31], is an ongoing primary prevention trial in the UK comparing 100 mg/day of aspirin versus placebo among men and women over 40 years of age who have either type 1 or type 2 diabetes but no past history of cardiovascular events (myocardial infarction or stroke).

Optimum dose of aspirin in the primary prevention of cardiovascular disease

The optimum dose of aspirin for the prevention of cardiovascular events remains controversial. The usual dose of aspirin used by clinicians worldwide is not based on the results of randomised controlled trials, which tried to identify the most efficacious or the safest dosage of aspirin. A wide range of doses of aspirin: 75 to 325 mg/day are used worldwide[32]. However, as little as 30 mg of aspirin daily is sufficient to fully inhibit platelet thromboxane production. The CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial confirmed the efficacy and safety of low-dose aspirin. [33] The CHARISMA (Clopidogrel for High Atherothombotic Risk and Ischaemic Stabilization, Management and Avoidance) trial studied more than 15,000 patients at high risk of cardiovascular events who were assigned clopidogrel or placebo with aspirin 75 to 162 mg/day. CHARISMA trial indicated that >100 mg/day of aspirin may cause harm compared with low doses (75 to 81 mg/day) and are also not associated with clinical benefits. Low dose daily aspirin not > 81 mg/day optimise efficacy as well as safety in patients receiving aspirin for long-term primary as well as secondary prevention, particularly in patients receiving dual antiplatelet therapy[34]. According to the US Preventive Services Task Force recommendations (2009), a dose of 75 mg/day of aspirin is as effective as higher doses with a lower risk of gastrointestinal bleeding[15].

Conclusion

Cardiovascular primary prevention begins with overall lifestyle modification, which includes a healthy diet, smoking cessation, strict blood pressure control, and regular physical activity. Low-dose aspirin may reduce the cardiovascular risk in asymptomatic individuals. However, detailed consideration of individual cardiovascular risk and the potential benefit versus harm of treatment should be assessed before starting long-term aspirin therapy. The role of aspirin in the primary prevention of major cardiovascular events or death in people with diabetes mellitus has been found to be lower and controversial as compared to other high-risk populations. The ADA recommends the use of 75 to 162 mg/day of aspirin for primary prevention in both type 1 and type 2 diabetics at increased cardiovascular risk (10 year risk > 10%). There is no substantial evidence that lower doses or modified release formulations of aspirin are associated with a lower risk of bleeding.

We clinicians may have responded too aggressively to low levels of cardiovascular risk in the general population and have probably over-prescribed aspirin to people who really did not require antiplatelet therapy but simply some lifestyle modifications.

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REVIEW ARTICLE

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Coronary artery disease in women: How does it differ from men?

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Abstract

It is not generally known that coronary artery disease (CAD) is quite common in women and that more women than men die of ischaemic heart disease every year. Also it has become clear in the past few years that CAD in women has many unique features which are not present in men. Obesity, metabolic syndrome, and diabetes disproportionately affect women. They demonstrate more symptoms and/or noninvasive findings suggestive of ischaemic heart disease, yet they have a lower prevalence of significant luminal obstruction compared to men. Women, especially the younger ones, have poorer outcomes. There are substantial delays in health care seeking behaviour and less use of treatment resources in case of women as compared with men. The timely diagnosis of CAD and assessment of potential risk of coronary artery disease in women are crucial steps towards improving outcomes. The physicians/cardiologists need to be made aware of the differences in the pattern of CAD in the two sexes so that complications can be prevented and optimal management strategies can be outlined.

Key words: Coronary artery disease, women.

Introduction

It is a myth that coronary artery disease (CAD) is less common and less severe in women. During the fertile age they do have a lower incidence of CAD, but after menopause the incidence is the same or higher. They tend to be 10 years older than men when they first experience an ischaemic episode. A 50-year-old woman's risk of dying from coronary artery disease is 10 times greater than her mortality risk from hip fracture and breast cancer combined. Although mortality from ischaemic heart disease (IHD) has declined in the recent years, the decline observed is of lesser magnitude in women as compared to men of a similar age[1]. It is generally not appreciated that the CAD follows a somewhat different pattern in women. The gender-based differences in the age of manifestation, risk factors, pathophysiology, clinical manifestations, and diagnosis of CAD need to be understood by the treating physician so that appropriate and timely treatment can be given.

Social factors and gender bias in treatment

Women tend to minimise their symptoms and have poorer psychosocial adjustment following a CAD event. Since research studies included very few women, the knowledge regarding heart disease in them is poor. Although substantial medical advances have improved outcomes following cardiac ischaemic events, they generally receive suboptimal and less-aggressive therapy. India and many other countries of the world are male dominated societies where females have lesser treatment resources, hence their treatment is delayed and incomplete. Women are less likely to have an ECG when they have an episode of ischaemic heart disease or chest pain. They are less likely to receive aspirin, beta-blockers, statins, antiarrhythmic treatment, thrombolytic therapy, Cardiac resynchronisation therapy (CRT), an implantable cardioverter defibrillator (AICD) and cardiac transplant strategies[2]. However the situation has improved somewhat in the recent years in the developed countries. Earlier, after abnormal noninvasive test results (US data) women were less likely to be referred for coronary angiography. Nowadays, once angiography has been undertaken, there is comparable referral for myocardial revascularisation for both genders in the US and the UK[3]. In fact, the major contributor to the increased survival among women since 2000 appears to be improved care of established cardiovascular disease rather than a decrease in the occurrence of new cases of cardiovascular disease in women, emphasising the need for preventive interventions. However, the situation is not the same in developing countries like India.

Gender differences in risk factors

In general, women consume an excess of fat and carbohydrates, do not exercise regularly and have less time to rest. Those presenting with CAD are more likely to have a history of diabetes mellitus, hypertension, and hyperlipidaemia than their male counterparts. While the risk factors for CAD are virtually the same in men and women, the impact of these risk factors is different for both sexes. Elderly hypertensive women and young female smokers are prominent at-risk subsets. Diabetes is a more powerful risk factor for women than for men[3].

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Diabetic females have significantly greater rates of ischaemic heart disease (IHD) mortality compared with diabetic men[4]. Diabetic women with myocardial infarction (MI) have a doubled risk of reinfarction and a four-fold greater likelihood of developing heart failure[3]. Diabetes is an independent risk factor for poor outcome of percutaneous interventions (PCI) in women more than men. Apple type obesity and metabolic syndrome are independent risk factor for CAD mortality more in women than men. According to some studies, low HDL (high-density lipoprotein cholesterol) levels, elevated triglyceride and Lp(a) (Lipoprotein A) levels are a stronger predictor of CAD risk in the fair sex[5].

Importance of cardiac biomarkers

In patients with acute coronary syndrome (ACS), men are more likely to have elevated creatine kinase MB and troponins, whereas women are more likely to have raised C-reactive protein (hsCRP) and brain natriuretic peptide (BNP)[6]. Inflammation is believed to have a role in the pathogenesis of cardiovascular events. Therefore, the measurement of inflammatory markers has been proposed as a method to improve the prediction of the risk of these events particularly in females. Newer markers like apolipoprotein E polymorphism and serum amyloid A levels are more important in women[6].

Differences in the pathophysiologic mechanisms

The exact pathophysiology of ischaemic heart disease in women is not known but many theories have been put forward. They develop a different form of vascular disease than men. Structurally, their coronary vessels appear to contain more diffuse atherosclerosis with involvement of the entire circumference of the artery and not localised plaques. These women, in response to atherosclerosis, "remodel" the entire artery so that the lining of the artery becomes thickened throughout, making the plaques flush with the wall of the artery ("female-pattern" coronary artery disease). On cardiac catheterisation, their coronary arteries appear smooth-walled and normal. Nearly 50% of women undergoing invasive evaluation do not have any flow-limiting coronary stenoses at angiography[7]. However, in such cases, the intravascular ultrasound (IVUS) examination revealed that > 80% of women with so-called "normal angiograms" have plaque lesions.

Whereas atherosclerotic plaque rupture, platelet-rich thrombus, and microembolisation may be operative more often in men, small-vessel disease and vascular inflammation may be operative more often in women[6]. Findings from the WISE study[8] have highlighted the pathophysiologic role of microvascular and endothelial dysfunction in CAD in females. On an average, they have coronary vessels 10% smaller than those of men. Functionally, their vessels frequently show impaired vasodilator responses[9]. In such women, an area of ischaemic injury may not be limited because the usual vasorelaxation required for collateral function is abnormal. This theory could help explain why they tolerate acute coronary syndrome (ACS) poorly compared with men and why subsequent heart failure, for example, is not only more frequent but also more lethal in women than men. However, objections have been raised to the above theories as convincing evidence is lacking.

Differences in symptoms

The syndrome of chest pain without obstructive coronary artery disease (CAD) is distinctly more common in women than in men. They are more prone to have atypical symptoms. Almost half of myocardial infarctions in women present with shortness of breath (SOB), nausea, indigestion, a burning sensation in the chest or upper abdomen, dizziness, sweating, vague fullness or fatigue. They are more likely to have neck, arms, back and shoulder pain. They also tend to experience anxiety and sleep disturbances, as initial cardiac symptoms. A recent study has observed that women reporting frequent angina were more likely to exhibit ischemia and this may characterise a female-specific typical angina pattern[10].

Myocardial infarction in women

For women, the initial manifestation of CAD is usually stable angina (47% in women compared to 26% in men) or unstable angina rather than enzyme or ECG-documented acute MI[11]. Among those with MI, fewer women than men had ECG-ST elevation MI, the subset appropriate for coronary thrombolysis. Pathologic evidence of MI may exist in the absence of obstructive CAD[12]. Women, in particular young ones (< 55 years), have a worse prognosis from acute MI than their male counterparts, with a greater recurrence of MI[13]. For a woman under 50 years of age, who has a myocardial infarction (MI), the mortality rate is approximately twice that for men. After MI they have greater prevalence of tachycardia and heart block. They also have higher rates of in-hospital complications from myocardial infarction, including strokes, bleeding, shock, and cardiac rupture. The difference does not occur in older women with MI. It is not clear why sex differences in the outcome of MI are seen in young and middle-aged patients but not older patients. A strikingly increased incidence of sudden cardiac death before reaching the hospital has been reported in younger women also (aged 35 to 44 years)[14].

An effective diagnostic strategy is critical in women at risk because up to 40% of initial cardiac events are fatal. Triple-vessel or left main CAD is more common in men, even though more women than men die from CAD. In contrast to these patients with STEMI (ST elevation MI), no sex differences are usually found among the patients with non–ST-segment–elevation MI after adjustment for risk factors. Women with unstable angina actually did better than men[15].

Coronary artery disease in younger women

Younger women who die suddenly of coronary thrombosis are often cigarette smokers although other risk factors may also contribute. They may have a hypercoagulable state, coronary spasms, or microvascular disease. They tend to have plaque erosion. The younger women have relatively little coronary arterial narrowing and less plaque calcium. Older women who die suddenly of coronary thrombosis are typically hyper-cholesterolaemic, have plaque rupture in contrast to plaque erosion, and have severe coronary arterial narrowing and far more plaque calcium[16].

Heart failure (HF) in women

HF most often occurs after ACS, longstanding hypertension, and diabetes. Post-MI heart failure has also increased more in women (46% as compared to 22% in men). Diastolic dysfunction is more common in women as compared to men (43% vs 23%)[17]. A new study found that women receiving cardiac resynchronisation therapy defibrillator (CRT-D) therapy to prevent heart failure progression had significantly better outcomes than men receiving the same therapy. Reduction of heart failure in females was twice that of males – 70 per cent versus 35 per cent[18].

Gender-specific optimised diagnostic strategies

In symptomatic women, noninvasive diagnostic studies (exercise ECG and cardiac imaging studies) are recommended for those who are at an intermediate to high pre-test likelihood of coronary artery disease[19]. These include women older than 50 years with risk factors like diabetes and metabolic syndrome. The exercise ECG has a lower sensitivity for women (with more false positives) than for men, which is compounded by the inability of many women to exercise to adequate intensity. Nonetheless, a true negative exercise ECG has high predictive accuracy for the absence of clinically significant CHD in women. On the whole, treadmill testing has lesser diagnostic value in women as compared to men. Myocardial perfusion imaging improves the diagnostic accuracy of exercise testing, with particular benefit of technetium 99m sestamibi SPECT imaging. Stress echocardiography in women shows comparable sensitivity and specificity to studies in men and is a valuable test as long as an adequate echocardiographic image can be obtained. It is advisable to follow a sequential approach to testing as it would be a more cost-effective diagnostic strategy[3].

Medical treatment and prevention of CAD in women

Timely and accurate diagnosis can significantly reduce CAD mortality in a women. Her risk for developing CAD should be determined before starting the treatment. The latest classification of cardiovascular disease (CVD) risk determination in women proposed by the American Heart Association (2011) is as follows[20]:-

The criteria for high-risk women (≥1 high-risk states) include clinically manifest (Coronary Heart Disease) CHD, clinically manifest cerebrovascular disease, clinically manifest peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic kidney disease, and diabetes mellitus.

The criteria for at-risk women (1 major risk factor[s]) are cigarette smoking, systolic blood pressure (SBP) 120 mm Hg, diastolic blood pressure (DBP) 80 mm Hg, or treated hypertension, total cholesterol 200 mg/dL, HDL-C < 50 mg/dl, or treated for dyslipidaemia, obesity, particularly central adiposity, poor diet, physical inactivity, family history of premature cardiovascular disease occurring in first-degree relatives in men < 55 years of age or in women < 65 years of age, metabolic syndrome, evidence of advanced subclinical atherosclerosis (e.g., coronary calcification, carotid plaque, or thickened intima-media thickness [IMT]), poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise, systemic autoimmune collagen-vascular disease (e.g., lupus or rheumatoid arthritis), history of pre-eclampsia, gestational diabetes, or pregnancy-induced hypertension.

Ideal cardiovascular health criteria are total cholesterol < 200 mg/dl (untreated); BP < 120/< 80 mm Hg (untreated); body mass index < 25 kg/m^2; abstinence from smoking; physical activity at goal for adults > 20 y of age: 150 min/week moderate intensity, 75 min/week vigorous intensity, or combination; and healthy dietary approaches to stop hypertension (DASH)-like diet .

Guidelines for the prevention of cardiovascular disease

in women published by the *Journal of the American College Cardiology* (2011 update)[20] recommend that intervention intensity and treatment goals should be tailored to the overall risk; with those at highest risk receiving the most intense risk-lowering interventions. Women at high risk for CVD and without contraindications should receive aspirin, beta-blockers, and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, omega-3 fatty acids in the form of fish or in capsule form in addition to pharmacologic therapy for hyperlipidaemia, hypertension, and diabetes. Aspirin appears cost-effective in women $\geq$ 65 years of age with moderate to severe CVD risk. Cardiac rehabilitation is recommended in cases of recent cardiovascular event or procedure or symptoms of heart failure. Women who are at optimal or low risk for CVD should be encouraged to maintain or further improve their healthy lifestyle practices. They should be advised to consume a diet rich in fruits and vegetables; to choose whole-grain, high-fibre foods; to limit intake of saturated fat, cholesterol, alcohol, sodium, and sugar; and avoid trans-fatty acids and to exercise regularly. Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioural programme when indicated to maintain or achieve an appropriate body weight (e.g., BMI < 25 kg/m^2 in the US women), waist size (e.g., < 35 inches), or other target metric of obesity. Optimal application of these preventive practices significantly reduces the burden of death and disability caused by CAD in women. A thorough non-invasive assessment should be made for deciding specialised PCI/CABG procedures keeping in mind the other comorbid conditions. More and more females should be submitted to post-MI and post-CABG rehabilitation programmes. Dosage of unfractionated heparin, enoxaparin and glycoprotein IIb/IIIa inhibitors (like eptifibatide) have to be given less according to body weight, advanced age, and creatinine clearance, etc., because women are significantly more likely to be overdosed than men.

Results of myocardial revascularisation procedures in women

In-hospital mortality after CABG has been reported to be twice as high in women relative to men. They have more post-operative depression and relatively lower quality of life at 1-yr after CABG. In-hospital mortality of both primary PCI as well as elective PCI are also more in women than in men probably because they are older, have smaller arteries, and more concomitant diseases[3].

Why the gender differences?

The complete explanation of the unfavourable prognosis of younger women with myocardial infarction is far from elucidated. Is it a bias in patient-care patterns? Or is it a different disease with a more prominent microvascular/inflammatory component that provokes symptoms of ischaemia without obstructive coronary artery disease. It is possible that unaccounted comorbidities and risk factors are responsible for the outcome differences. Alternatively, other unknown factors may be involved; among these, social and psychological factors have rarely been considered. A recent study, for example, documented a remarkable decrease in mortality in women with coronary heart disease randomly assigned to a stress-reduction intervention specifically tailored to women[21].

Role of hormone replacement therapy (HRT)

Oestrogen helps in cardioprotection by improving endothelial function and by decreasing inflammation in the vessel wall. Oestrogen deficiency increases the progression of atherosclerosis. Initial observational studies in the late eighties and early nineties had shown the role of HRT in women for protection against CAD and its complications. However, the subsequent randomised controlled trials like WHI have shown that instead of cardioprotection, HRT may be causing more CAD and its sequelae on long-term use especially in late onset cases. The suggestion from the women's health initiative (WHI) study that oestrogen intervention at or shortly after the menopause may be protective[22] now known as the "critical timing" hypothesis warrants further investigation. At present, HRT cannot be routinely recommended for cardioprotection against CAD in women.

Conclusions

CAD in women represents an important problem that is difficult to identify early, owing to our incomplete understanding of the disease mechanisms. There is a need for recognising CAD as a major public health issue in women so that outcomes can be improved in future with timely medical management. The atypical presentations, the unique risk factors, and more frequent normal coronaries on angiography should be kept in mind. More research is needed to explore these sex-related differences so that optimal gender specific diagnostic and mangement strategies can be developed.

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"The physician prescribes hesitatingly out of his few resources. If the patient mends, he is glad and surprised."

– Ralph Waldo Emerson (1803-1882).

REVIEW ARTICLE

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Osteoarthritis of the knee joint: An overview

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Abstract

Knee osteoarthritis (OA) is a disorder of cartilage and periarticular bone. It is a most frequent chronic musculoskeletal disorder and the leading cause of disability in the elderly. The risk factors include genetics, female sex, past trauma, advancing age, and obesity. A plain radiograph may help in the diagnosis of knee OA. The management of OA primarily comprises pharmacological therapy and various non-pharmacological interventions. Total joint replacement of the knee OA is recommended for patients with chronic pain and disability despite maximal medical therapy. This review focuses on the diagnosis, pathogenesis, and treatment based on recent studies.

Key words: Knee; osteoarthritis; treatment; conservative.

The knee joint is quite a complex type of synovial joint. It has three compartments, namely – medial, lateral, and patellofemoral. Four major ligaments within the knee (anterior and posterior cruciate ligaments), and on the inner and outer sides of the knee (medial and lateral collateral ligaments) stabilise the joint along with the capsule. The anterior and posterior cruciate ligaments provide front and back (anterior and posterior) and rotational stability to the knee. The medial and lateral collateral ligament located along the inner (medial) and outer (lateral) sides of the knee provide medial and lateral stability to the knee. Fibrocartilaginous structures called menisci line the top of the tibia and lie between the tibial and the femoral condyles. Menisci provide space, stability, and cushion for the knee joint[1].

The main function of knee joint is to bend and straighten for moving the body. The knee is more than just a simple hinge. It also twists and rotates. In order to perform all of these actions and to support the entire body while doing so, the knee relies on a number of structures, including bones, ligaments, tendons, and cartilage[1].

Knee pain is one of the most common musculoskeletal complaints that bring people to their physician. With today's increasingly active society, the number of knee problems is increasing. Knee pain has a wide variety of causes and treatments. Causes of knee pain include injury, degeneration, arthritis, infrequently infection, and rarely bone tumours. Osteoarthritis of the knee joint is most common and is discussed here.

Osteoarthritis (OA) also known as degenerative arthritis or degenerative joint disease or osteoarthrosis, is a group of mechanical abnormalities involving degradation of joints, including articular cartilage and subchondral bone[2]. The word 'osteoarthritis' originated from the Greek word "osteo", meaning "of the bone", "arthro", meaning "joint", and "it is", meaning inflammation, although the "it is" of osteoarthritis is somewhat of a misnomer – inflammation is not a conspicuous feature which is present in rheumatoid or autoimmune types of arthritis. Some clinicians refer to this condition as osteoarthrosis to signify the lack of inflammatory response[3].

Osteoarthritis traditionally was considered as a disease of articular cartilage. Now it is thought to involve the entire joint tissues, synovium, capsule, bone and ligaments leading to subchondral bone attrition and remodelling, meniscal degeneration, ligamentous laxity, fat pad extrusion, and impairments of neuromuscular control. The cartilage is poorly innervated and is not the cause of pain. The diagnosis must be made clinically because laboratory test may not be helpful and radiological findings do not necessarily correlate with the symptoms[2,4].

OA is the most common form of arthritis[5]. It is among the most prevalent and disabling chronic conditions in the United States[6]. The prevalence increases with age, and by the age of 65, approximately 80 percent of the US population is affected[7]. More than half of those with arthritis are under 65 years of age. Nearly 60% of Americans with arthritis are women. Indian data in this regard is lacking. It is difficult to estimate the prevalence of osteoarthritis because there are no universally applicable criteria for its diagnosis. Radiographic and symptomatic knee OA in adults 45 years or older was prevalent in 19% and 7% of Framingham subjects, respectively, and in 28% and 17% of Johnston county subjects, respectively[8,9]. The overall number of US adults affected by OA in any joint clearly has increased during recent decades due to aging of the population and the increasing prevalence of obesity[10].

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Risk factors

OA knee increases with age (older than 50 years), especially in women. According to a number of published reports, anywhere from 6% to over 13% of men, but between 7% and 19% of women, over 45 years of age are affected, resulting in a 45% less risk of incidence in men[11].

Additional factors that increase the risk of developing OA of the knee include genetics and obesity[12-17]. Genetic factors appear to influence risk of developing primary OA though they may influence disease differently in men and women. Twin studies suggest that generalised OA in women has a heritability rate of 39 to 65%, with a concordance rate in monozygotic twins of 0.64.

Other risk factors includes joint hypermobility or instability, specific occupations, or sports stress (e.g., with high impact loading with farming or soccer), peripheral neuropathy, injury to the joint, history of immobilisation, repetitive knee bending or heavy weight lifting, and strong family history[18-20]. Other causes are lower extremity misalignment, torn meniscal pathology, bone marrow lesion shown by MRI, and quadriceps weakness.

Research has shown not only that OA involves all joint structures but also that biomechanics play a major role in the onset and progression of this disease.

Classification

Osteoarthritis can be classified into either primary or secondary depending on whether or not there is an identifiable underlying cause.

Signs and symptoms

Although any joint in the body can be affected by OA, the knee joint is more commonly involved especially in the Indian sub-continent. Pain is the first and predominant symptom, causing loss of ability and often stiffness. "Pain" is generally described as a sharp ache, or a burning sensation in the associated muscles and tendons. The pain is intermittent and is worse with use and better with rest. The stiffness generally improves after 30 minutes of activity unlike the prolonged (usually > 30 min) stiffness caused by rheumatoid arthritis. Humid and cold weather increases the pain in many patients. As OA progresses, the affected joints appear larger, are stiff and painful, and usually feel better with gentle use but worse with excessive or prolonged use, thus distinguishing it from rheumatoid arthritis. OA of the knee can cause a crackling noise called "crepitus", when the affected joint is moved or touched, and patients may experience muscle spasm and contractions in the tendons. Occasionally, the patient presents with swelling or joint effusion sometimes called water in the knee in lay terms due to fluid within the joint. Poplitial cyst also known as Baker's cyst can also be seen with knee OA. In advanced cases, patients may present with lateral instability symptoms due to degenerated tears in cruciate ligaments and menisci or genu valgum (knock knee) or varum (bow-leg). Varus deformity is more common than valgus deformity because the medial compartment of the knee is more commonly involved.

In smaller joints, such as at the fingers, hard bony enlargements due to hypertrophic changes, called Heberden's nodes (on the distal interphalangeal joints) and/or Bouchard's nodes (on the proximal interphalangeal joints), may form, and though they are not necessarily painful, they do limit the movement of the fingers significantly. There may be tenderness at the carpometacarpal joint of the thumb especially in females. OA at the toes leads to the formation of bunions, rendering them red or swollen. Hallux rigidus and hallux valgus deformity are common due to involvement of first metatarsophalangeal joint. Some people notice these physical changes before they experience any pain. In the larger joints like shoulder and hip, pain and limitation of movement usually occur. In the shoulder, external rotation is commonly affected, while in the hip, internal rotation is restricted. In the spine, pain and limitation of movement is a usual finding. Patients may present with neurological deficits or symptoms of neurological claudication due to impingement of nerve roots or canal stenosis[21,22].

Causes

1. **Primary OA**

   Primary osteoarthritis is a chronic degenerative disorder related to but not caused by aging, as there are people well into their nineties who have no clinical or functional signs of the disease. The pathophysiology of osteoarthritis involves a combination of mechanical, cellular, and biochemical processes[23]. The interaction of these processes leads to changes in the composition and mechanical properties of the articular cartilage. Cartilage is composed of water, collagen, and proteoglycans. As a person ages, the water content of the cartilage decreases as a result of a reduced proteoglycan content, thus causing the cartilage to be less resilient. Without the protective effects of the proteoglycans, the collagen fibres of the cartilage can become susceptible to degradation and thus exacerbate the degeneration. Inflammation of the surrounding joint capsule can also occur, though often mild (compared to what occurs in rheumatoid arthritis). This can happen as breakdown products from the cartilage are released into the synovial space, and the cells lining

the joint attempt to remove them. New bone formation, called "spurs" or osteophytes, can form on the margins of the joints, possibly in an attempt to improve the congruence of the articular cartilage surfaces. These bone changes, together with the inflammation, can be both painful and disabling[23].

2. **Secondary OA**[24]:

This type of OA is caused by other factors but the resulting pathology is the same as for primary OA, i.e.,

- Congenital or developmental disorders of joints
- Mechanical: limb length discrepancy, malalignment, hyper-laxity, Ehlers-Danlos syndrome, Marfan's syndrome
- Inflammatory: rheumatologic diseases, i.e., rheumatoid arthritis, SLE, all chronic forms of arthritis
- Traumatic: injury to joints or ligaments, post-surgical
- Infective: septic arthritis, Lyme disease
- Metabolic: haemochromatosis and Wilson's disease, gout, calcium crystal deposition, alkaptonuria
- Endocrine: diabetes, acromegaly, hypothyroidism, obesity
- Neuropathic arthopathy
- Miscellaneous: haemophilia, osteonecrosis

Diagnosis

Diagnosis is made with reasonable certainty based on the history and clinical examination. X-rays may confirm the diagnosis. The main characteristics of osteoarthritis are changes in the subchondral bone. The radiographic hallmarks of primary osteoarthritis includes: asymmetrical joint space narrowing or loss, subchondral sclerosis (increased bone formation around the joint), subchondral cyst formation, and osteophytes. The initial radiographs may not show all of the findings. However, in early osteoarthritis, minimal no uniform joint space narrowing may be the only radiographic finding. As the disease progresses, the series of above changes followed by lateral subluxation of tibia and in very advanced stage collapse of the joint may occur[23].

In patients with osteoarthritis of the knee, AP and lateral radiographs in standing position allow an adequate evaluation of the medial and lateral joint spaces. Follow-up radiographs are unnecessary in evaluating progression of the OA but can be helpful, especially if surgery is planned or a fracture is suspected.

Kellgren and Lawrence (K-L) classification has been developed as a radiological grading of osteoarthritis for knee, hip, hand, and other joints. It determines the severity of radiographic OA on the basis of the presence and degree of osteophytosis, joint-space narrowing (JSN), sclerosis, and deformity affecting the tibiofemoral joint. Radiographic OA of the knee usually is defined as a K-L grade of 2 or higher[25].

Plain films may not correlate with the findings on physical examination or with the degree of pain. Usually other imaging techniques are not necessary to clinically diagnose osteoarthritis.

Management

The principle of managing OA is reduction of pain, stiffness, and maintenance or improvement of function, retarding the disease's progression of joint damage and improvement of quality of life. There are three treatment modalities: non-pharmacological, pharmacological, and surgical. The approach to treatment should be tailored to specific patients because OA is heterogenous, involves different joints, and ranges in severity from mild to severe. Symptoms of OA can be reduced by providing the patient with information about the disease, its symptoms, progression, the goals of its treatment, and the importance of changes in lifestyle such as weight reduction and exercise. Weight reduction is quite effective and recommended for overweight or obese patients especially in symptomatic knee OA. It reduces the pain and improves physical function. It can be accomplished through an intensive low calorie diet programme. These lifestyle changes must be continued throughout life[26].

Exercise

Exercises that strengthen muscles and improve aerobic condition are most effective for osteoarthritis. Systematic reviews show that both aerobic and strengthening exercise programmes, produce only modest gain in measures of decreasing pain, improving disability and physical performance[27, 28]. Water- or land-based exercise, aerobic walking, quadriceps strengthening, resistance exercise, and tai chi reduce pain and disability from knee osteoarthritis[29-32].

Bracing and orthosis

Bracing of the knee or the foot can be a useful nonoperative and nonpharmacologic treatment for persons with osteoarthritis that predominantly involves either the medial or lateral tibiofemoral compartment. The aim of (medial or lateral wedged insoles and realigning knee braces is to reduce articular contact stress in the more involved tibiofemoral compartment. Immobiliser or

"rest" braces are not good long-term solutions for a chronic disease such as knee OA, because they may result in weakening of the quadriceps muscle.

The Osteoarthritis Research Society International and the American College of Rheumatology recommend the use of laterally wedged insoles for medial compartment knee OA. It reduces the relative load on the medial compartment and symptoms in at least some patients with mild or moderate medial compartment knee OA[33,34].

Knee sleeves provide warmth and mild compression and are effective in early knee OA. These do not enhance joint stability[35].

Corrective or realignment braces are more effective in moderate or severe OA. These have greater benefits and reduce compressive loading of the more affected joint compartment.

These also improved proprioception and quadriceps strength. Contraindications to bracing include flexion contracture of more than 10°, peripheral vascular disease, or intractable contact dermatitis[36].

Ice and diathermy

For theoretical reasons, ice may be expected to help reduce the local inflammatory component with OA flares. Similarly many patients are benefited from therapeutic heat. A Cochrane review showed that ice massage compared to control had a statistically beneficial effect on ROM, function and knee strength. Cold packs decreased swelling. Hot packs had no beneficial effect on oedema compared with placebo or cold application. Ice packs did not affect pain significantly, compared to control, in patients with OA[37].

Pharmacological treatment

Acetaminophen/paracetamol is the first-choice oral analgesic for mild osteoarthritis because of its safety and effectiveness. It has only mild adverse effects. There is less gastrointestinal (GI) discomfort associated with using NSAIDs. Liver toxicity is extremely rare but caution should be taken especially in alcoholics[38]. Non-steroidal anti-inflammatory drug (NSAID) is added or substituted if patient failed to respond or has little effect.

NSAIDs : The lowest dose for the shortest duration possible is used in order to minimise the occurrence of adverse events. A randomised, double-blind, controlled trial for treatment of OA with continuous versus intermittent celecoxib showed almost 50 per cent reduction in the rate of 'flares' in the continuous group over the 6-month treatment period[39]. NSAIDs are commonly used as second-line agents in patients with moderate or severe pain due to OA. These can be started at low doses, which can be increased if the pain control remains inadequate after 2 to 4 weeks. Their use should be limited to short-term, to help control episodic painful flares. Selective NSAIDs like COX-1 and COX-2 inhibitors play an integral role in gastric mucosa protection. According to *AJR* guidelines, COX-2 inhibitors should be used as a second-line medication after acetaminophen, especially for patients with GI risk factors. Recently, in patients without cardiac risk factors, COX-2 inhibitors can be used after acetaminophen fails to produce response. Celecoxib (Celebrex) is the most commonly used but has side effects like myocardial infarction and stroke[40-42].

The use of opioids should be limited to the patients who have contraindications or have ineffective response to acetaminophen and NSAIDs (*AJR* guidelines). Tramadol is the most commonly used agent alone or in combination for the treatment of moderate or severe OA. Codeine is also effective for OA pain. Opioids can cause hypersomnolence, constipation, and rarely delirium – especially in the older patients – therefore, close monitoring is required when using these agents. Non-tramadol opioids should not be routinely used, even if osteoarthritic pain is severe, due to risk of adverse events[43,44].

Topical creams

Topical creams are used as adjuvant therapy or even as a substitute for oral medications for OA pain. A recent meta-analysis of these agents found that patients using topical NSAIDs were twice more likely to accrue benefit than those using placebo. Topical medications include balms, creams, oils, gels, patches, solution forms – lotions, ointments, and other products that can be applied to the skin. The gel is approved by the US Food and Drug Administration (FDA) for OA. Most are available OTC (over-the-counter). Topical products may provide pain relief in mild arthritic pain that affects only a few joints. Diclofenac is one of the more commonly used topical NSAID preparation. Dry skin is the most common adverse event[45-47].

Tropical capsaicin is effective at 0.025% four times a day or 0.075% twice a day for OA pain. It depletes substance P from unmyelinated nociceptive C fibres. A systemic review by Mason *et al* showed that it is statistically more effective than placebo, but less effective than topical NSAIDs[48]. Local burning sensation is a well known complication after its use.

Other over-the-counter (OTC) topical pain medications are:-

- Counter-irritants – contain menthol, eucalyptus oil, or oil of wintergreen, and work by irritating the skin

where it is applied.

- Salicylates – are the main ingredient in topical analgesics. Creams which contain salicylates offer pain relief and reduce joint inflammation.

Other drugs

Glucosamine: Glucosamine and chondroitin are members of a group of dietary supplements often termed "complementary agents", "disease-modifying agents", or "disease-modifying osteoarthritis drugs" (DMOADs). They are derived from animal cartilage or crab shells. They relieve knee pain and perhaps repair the cells that line the joint. The therapeutic effects of glucosamine are studied in animals or *in vitro* models without confirmation in humans. The effect is possibly the result of its anti-inflammatory activity, synthesis of proteoglycans, and inhibition of the synthesis of proteolytic enzymes. It also stimulates synovial production of hyaluronic acid[49].

Controversy surrounds glucosamine. However, it remain popular even after the well-powered NIH-sponsored glucosamine/chondroitin arthritis intervention trial (GAIT) reported by Clegg *et al* in 1,500 patients showed little benefit from these agents at 2 years when used individually or in combination[49]. A 2010 meta-analysis by Wandel *et al* which included 10 trials that focussed on OA of the hip and knee in more than 3,800 combined patients has found that it is no better than placebo[50]. The Osteoarthritis Research Society International (OARSI) recommends that glucosamine be discontinued if no effect is seen following 6 months of administration[41]. Recently, Durmus found no additional effect of glucosamine in delaying the radiological progression and relieving the symptoms of OA[51]. In the United States, glucosamine is not approved by the Food and Drug Administration for medical use in humans. Since glucosamine is classified as a dietary supplement in the US, safety and formulation are solely the responsibility of the manufacturer. In most of Europe, glucosamine is approved as a medical drug and is sold in the form of glucosamine sulfate. The most common adverse effect of oral glucosamine sulfate (1,500 mg daily) is epigastric pain or tenderness[50].

Diacerein: An oral interleukin-1α inhibitor is reported to have slow-acting, but persistent, symptomatic relief in patients with osteoarthritis. A meta-analysis including systematic searches of the bibliographic databases Medline, Embase, Cinahl, Chemical Abstracts, Cochrane and Web of Science for RCTs concerning diacerein treatment of OA showed that it may be an alternative therapy for OA in patients who cannot take paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) because of adverse effects or lack of benefit. Diarrhoea is the most common side-effect; the symptomatic benefit of diacerein after 6 months remains unknown[52].

Nutraceuticals: Such as collagen hydrolysates (CHs) and avocado-soybean unsaponifiables (ASUs) are reported to be useful in OA treatment. Collagen hydrolysates showed significant improvement in pain and function. Avocado-soybean unsaponifiables have demonstrated positive results with respect to decreased NSAID use in several studies and functional and pain end-points in most of the reviewed studies[53].

There are other nutraceuticals like vitamins A, C, E , ginger, turmeric, and omega-3 fatty acids. These are widely used, but evidence did not recommend use of: vitamin E alone; vitamins A, C, and E in combination; ginger; turmeric; or Zyflamend for the treatment of OA or RA; or omega-3 fatty acids for OA[53,54].

Doxycycline: Pre-clinical data suggest that doxycycline might act as a disease-modifying agent for the treatment of osteoarthritis, with the potential to slow cartilage degeneration. Recent analysis shows that the symptomatic benefit of doxycycline is minimal to non-existent, while the small benefit in terms of joint space narrowing is of questionable clinical relevance and outweighed by safety problems[60].

Newer drugs

There are several new OA therapeutics in development that are directed toward pain relief as well as others with the potential to reduce or stop the progression of the disease.

Centrally acting agents: In 2010, the US Food and Drug Administration has approved Duloxetine, a serotonin norepinephrine reuptake inhibitor, for the treatment of chronic pain in patients with knee OA. Duloxetine is efficacious and tolerable in a dose of 60/120 mg/day. The only side-effects are nausea, dry mouth, constipation, fatigue, and decreased appetite. Recent studies supports the use of duloxetine as an adjunctive therapy in knee OA patients with an inadequate response to oral NSAIDs[55,56].

Anti-nerve growth factor tanezumab: It is a monoclonal antibody used as a biologic agents in patients with OA. It binds and inhibits nerve growth factor, and appears to relieve joint pain enough to improve function in people with moderate-to-severe hip and knee OA. Osteonecrosis is the serious side-effect following its use. The FDA is reviewing the safety of tanezumab that could still emerge as an effective treatment for the pain of osteoarthritis. Recently, the safety and efficacy of tanezumab in Japanese

patients has been studied[57].

S-adenosylmethionine (SAMe): SAMe is more effective than placebo in improving pain and stiffness related to osteoarthritis. S-adenosylmethionine is as effective as nonsteroidal anti-inflammatory drugs in reducing pain and disability from knee osteoarthritis. Side-effects include occasional gastrointestinal disturbances, mainly diarrhoea[58,59].

Intra-articular injections of hyaluronan or steroid are sometimes given when oral medications or other basic osteoarthritis therapies are not tolerated or sufficient.

Intra-articular hyaluronan (500-730 kDa sodium hyaluronate: It provides short-term symptomatic relief. Its use has been limited by cost, difficulties of administration, and conflicting evidence of efficacy. Recent studies in Asian patients with osteoarthritis of the knee suggests five weekly intra-articular injections of sodium hyaluronate are well tolerated, can provide sustained relief of pain, and can improve function. Now single doses of sodium hyaluronate are also available commercially[61-63].

Injection of glucocorticoids (such as hydrocortisone: It leads to short-term pain relief that may last between a few weeks and a few months. Two or three intra-articular steroidknee injections of 40 mg of triamcinolone acetonide are usually required. The possible long-term effects and the unpredictable duration are controversial and matters of debate[64].

The addition of steroid with viscosupplementation only improves first-week symptom and functional scores of viscosupplementation, but not beyond. The repeated use of corticosteroids especially could facilitate tissue atrophy, joint destruction, or cartilage degeneration[65-67]. Oral steroids are not recommended in the treatment of OA because of their modest benefit and high rate of adverse effects.

Platelet-rich plasma (PRP): Recently, PRP is being considered as an innovative and promising tool to stimulate repair of the damaged cartilage[68]. PRP is defined as an autologous concentration of human platelets in a small pool of plasma. It consists of many growth factors proved to be actively secreted by platelets to initiate mesenchymal tissue healing. PRP is a pool of growth factors stored in the granules of platelets, which have been found to take part in the regulation of articular cartilage. PRP may help in the treatment of degenerative lesions of articular cartilage and OA. There are only a few studies of PRP treatment for cartilage on osteoarthritic knees[69]. Comparison analysis also has been done between PRP and viscosupplementation hyaluronic acid for the treatment of knee cartilage degenerative lesions and OA. It has been found out that autologous PRP injections showed more and longer efficacy than hyaluronic acid injections in reducing pain and symptoms and recovering articular function[70-71]. Better results were achieved in younger and more active patients with a low degree of cartilage degeneration in comparison to more degenerated joints and in older patients[71].

Complementary and alternative medicine in osteoarthritis

Acupuncture

Acupuncture may provide some benefit in persons with knee osteoarthritis; however, the evidence is weak. Sham-controlled trials show statistically significant benefits. However, these benefits are small, do not meet our pre-defined thresholds for clinical relevance, and are probably due at least partially to placebo effects from incomplete blinding. Waiting list-controlled trials of acupuncture for peripheral joint OA suggest statistically significant and clinically relevant benefits, much of which may be due to expectation or placebo effects[72].

Transcutaneous electrical nerve stimulation (TENS)

While transcutaneous electrical nerve stimulation (TENS), interferential current stimulation, and pulsed electrostimulation have been used for twenty years to treat osteoarthritis in the knee, TENS uses electrical currents applied to the skin surrounding the knee. It was developed for instant pain relief and is applied by physiotherapists, or by patients themselves at home. A Cochrane review of studies determined that there is no evidence to show that it reduces pain or disability[73]. In contrast to the Cochrane review, a recent meta-analysis shows electrostimulation seemed to have a large effect on pain relief, moderate improvement on function, and with no evidence that it is unsafe[74].

Therapeutic ultrasound

Therapeutic ultrasound is widely used for its potential benefits on both knee pain and function, which may be clinically relevant. Therapeutic ultrasound may be beneficial for patients with osteoarthritis of the knee[75].

Hydrotherapy

It is a non-invasive, non-interventional, reasonably priced, therapeutic option with few side effects, in the concomitant treatment of osteoarthritis of the hip or knee[76].

Mud pack therapy

It is considered as an alternative and effective therapy in

the clinical management of knee OA. Studies with better methodology are needed to prove its scope[77].

Balneotherapy (mineral baths)

Balneotherapy or spa-therapy is an ancient and popular therapy. It involves spending time in an indoor pool filled with mineral water at temperature of between 31 to 34 degrees Celsius (88 to 93 degrees Fahrenheit). There is not enough data to tell if spending time in mineral baths has any effect on a person's physical function or quality of life. Balneotherapy can represent a useful back-up to pharmacological treatment of knee OA or a valid alternative for patients who do not tolerate pharmacological treatments[78,79].

Low-level laser therapy

When associated with exercises, it is effective in yielding pain relief, function due to its photochemical effect[80].

Moxibustion

It may be effective in symptom management in patients with knee OA, but evidence supporting this conclusion is limited[81].

Surgery

Joint lavage does not result in a relevant benefit for patients with knee osteoarthritis in terms of pain relief or improvement of function[82]. Arthroscopic surgery of the knee is commonly done in middle-aged patients, on suspicion of a meniscus tear or osteoarthritis. Arthroscopic surgical intervention for osteoarthritis of the knee has no benefit[83]. High tibial osteotomy HTO improves knee function and reduces pain, but there is not enough evidence to be certain of these results. Correction osteotomy is to transfer the load bearing from the pathologic to the normal compartment of the knee. A successful outcome of the osteotomy relies on proper patient selection, stage of osteoarthritis, achievement and maintenance of adequate operative correction. It is not known whether an osteotomy (valgus high tibial osteotomy) is better than no surgery at all[84].

If the conservative management is ineffective, joint replacement surgery or resurfacing may be required in advanced cases. The main indication for total knee arthroplasty is relief of pain with or without deformities associated with knee osteoarthritis. Evidence supports joint replacement for both knees and hips[85].

The future

Several recent studies have greatly advanced the development and preclinical evaluation of potential stem cell-based treatments for osteoarthritis through novel approaches focussed on cell therapy, tissue engineering, and drug discovery but knowledge on this topic is still preliminary. More randomised controlled trials are needed to support the potential of this biological treatment for cartilage repair[86,87].

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CASE REPORT

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Metastatic choriocarcinoma with recurrent intracranial haemorrhage

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Abstract

Choriocarcinoma is uncommonly seen after normal gestation.The authors report a case of metastatic choriocarcinoma in a 25-year-old female presenting atypically as an intracranial haemorrhage on NCCT head. MRI of the brain revealed multiple new haemorrhages with CECT chest showing lung metastases along with elevated beta hcg levels and endometrial tissue showing Arias-Stella reaction on histopathological examination, confirming the diagnosis of a metastatic choriocarcinoma presenting as occult primary.

Key words: Choriocarcinoma, intracerebral haemorrhage, Arias-Stella reaction.

Introduction

Choriocarcinoma, is a gestational trophoblastic disease, seen in young females and is associated commonly with molar pregnancy. It usually disseminates haematogenously to the lungs, vagina, brain, kidney, and ovaries with the obvious primary in the uterus. This case report describes a patient with choriocarcinoma presenting atypically as a case of intracerebral haemorrhage manifesting as chronic headache with multiple brain and lung metastases without evident primary focus in the uterus.

Case report

A 25-year-old female was referred to the Department of Medicine as a case of intracerebral haemorrhage in the right parietal region on noncontrast computed tomography (NCCT) of head with unknown aetiology. She presented with complaints of severe, persistent headache accompanied by nausea and vomiting for the past 1 month.There was no history of any weakness, visual and speech disturbances, seizures, or alterated behaviour. There was no significant family or past history, but the obstetric history revealed that the patient had intrauterine death at 8-months of pregnancy, about 4 months before the presentation, with the cause being unknown. The patient also had a history of bleeding per vaginum for the past 1 ½ months.

On admission, the patient was conscious and oriented with stable vitals and had no focal neurological deficit with higher mental functions, motor, sensory and cranial system examination being normal. Her cardiovascular, respiratory, and abdominal systems were also normal. Gynaecological examination revealed normal per vaginum examination findings.

A magnetic resonance imaging (MRI) brain scan and

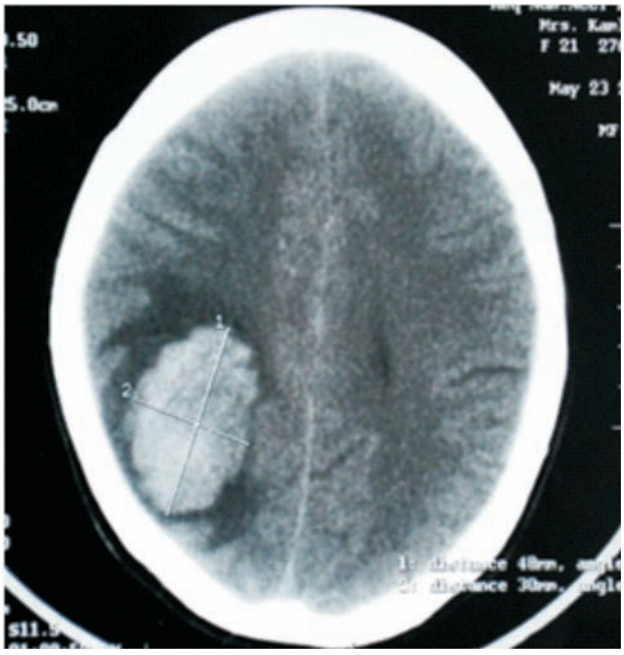

Fig. 1: *Noncontrast computed tomography (NCCT) head of the patient showing CT hyperdense area in the right parietal region with surrounding white matter oedema suggesting intra-cerebral haemorrhage (ICH).*

magnetic resonance angiography (MRA) were done to locate the site of bleed with MRI brain showing multiple newly developed haemorrhagic spots in the posterior parietal region compared with the previous noncontrast computed tomography (NCCT) head with magnetic resonance angiography images being normal. A magnetic resonance venography done to exclude haemorrhagic cortical venous thrombosis and normal.

To rule-out coagulopathies, prothrombin time (PT), activated partial thromboplastin time (APTT), serum anti-nuclear antibody (ANA) levels were estimated and were

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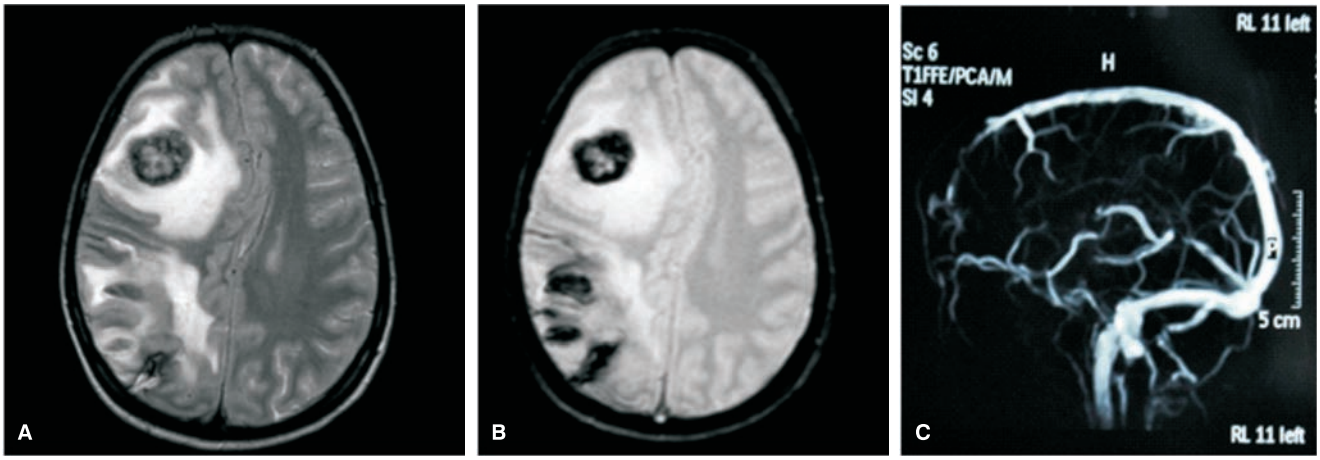

Fig. 2: *Magnetic resonance imaging (MRI) and magnetic resonance venography (MRV).* ***A.*** *T2-weighted axial image of the patient shows heterogenous intensity area of central hyperintensity area with surrounding hypointensity in right parietal region with extensive white matter oedema;* ***B.*** *FFE T2 imaging shows blooming at the respective regions suggesting intracranial haemorrhage;* ***C.*** *MR venography of the patient showed no abnormalities.*

found to be normal. Platelet counts, peripheral blood film detailed study, and D-Dimer levels along with 2-D echocardiography and ultrasonography of abdomen revealed no abnormalities.

The fact that the patient was of child-bearing age and had an intra-uterine death (IUD) 4 months back with the cause of intra uterine death being unknown, led us to estimate her serum beta-hCG level which was found to be elevated to the tune of 4,34,400 mIU/ml which led to the suspicion of choriocarcinoma metastasising to the brain. Dilatation and curettage of endometrial tissue was done and examination of the tissue on histopathological examination showed Arias-Stella reaction. The changes of the reaction are a histological clue to the presumptive diagnosis of the presence of chorial tissue in cases in which the chorionic material is not found in the endometrial biopsy.

The main characteristic of the reaction is enlargement, of the nucleus to double or many times the normal size. Hypertrophied nuclei can show an ovoid or round shape with granular or vesicular viable chromatin, an irregular outline, and a hyperchromatic appearance or a compact, pyknotic pattern (Fig. 3).

Furthermore, contrast-enhanced computed tomography (CECT) chest scan was done and it revealed multiple metastatic deposits in both lung fields, confirming the

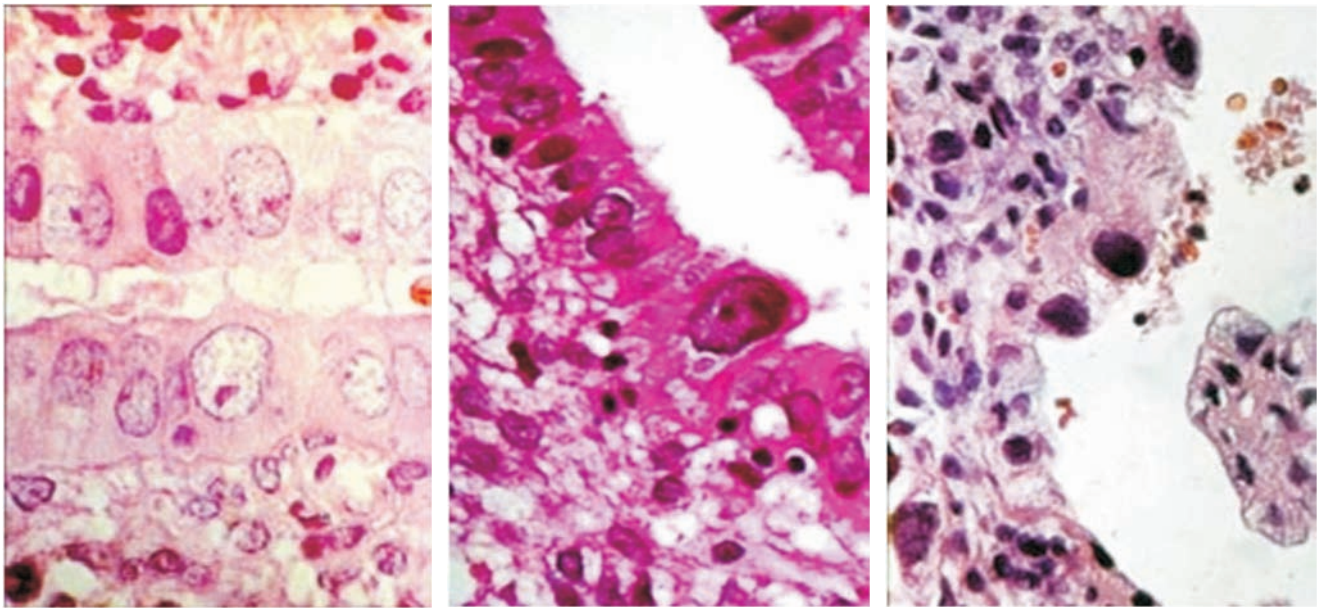

Fig. 3: *Endometrial biopsy showing Arias-Stella reaction.*

presence of choriocarcinoma with multiple metastatic deposits in lung and brain, with choriocarcinoma being the cause of recurrent, multiple, intracerebral haemorrhages (ICH).

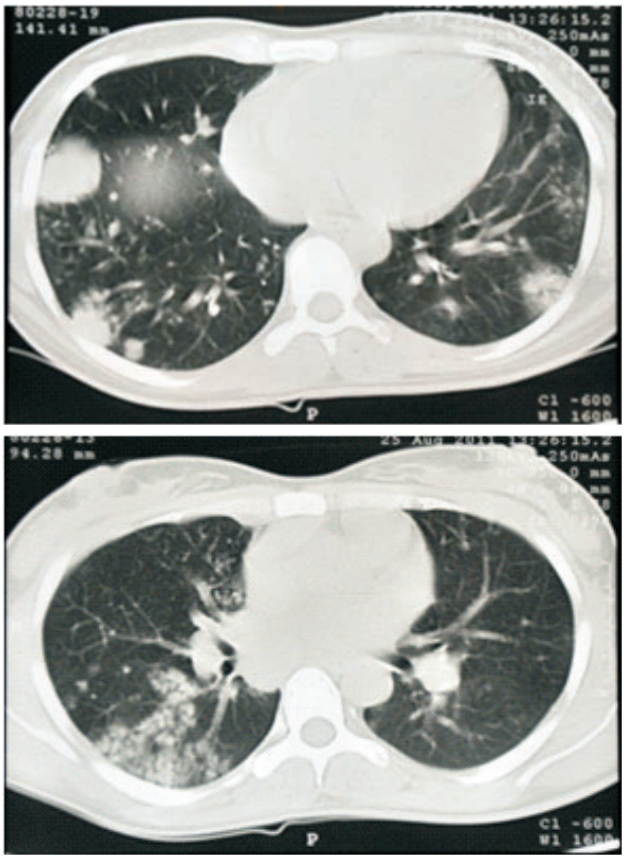

Fig. 4: *Contrast-enhanced computed tomoraphy (CECT) chest of the patient shows multiple heterogenously enhancing opacities sen in both lung fields suggesting metastatic lesion. The patient improved after chemotherapy and radiotherapy.*

Discussion

Our case was rare in several ways. Firstly, a young patient presented with recurrent intra-cerebral haemorrhages at multiple sites. Secondly, no obvious primary focus in the biopsy was found. In literature,very few cases of metastatic choriocarcinomas are reported without evidence of choriocarcinoma in the pelvic cavity suggesting that these pelvic tumours can often regress after metastasis[9].

Choriocarcinomas are a malignant neoplastic form of the trophoblastic tissue with a tendency for early metastasis[1]. The tumour metastasises first to the lung and to the brain[2]. This often happens months after molar pregnancy or abortion.The incidence of choriocarcinoma after a normal pregnancy is 1 in 50,000 live births[3]. Cerebral metastasis occurs in 10 - 20% patients with choriocarcinoma[4]. Choriocarcinoma with cerebral metastasis have been associated with cerebral haematoma, arterial aneurysms, and embolic vascular occlusions[5]. The trapped neoplastic cells, in the form of emboli in the cerebral circulation, invade the vessel wall resulting in haemorrhage within the tumour or a partial disruption of the vessel wall that can lead to aneurysm formation and subsequent haemorrhage[7,8]. The most common cause of intra-cerebral haemorrhage is probably aneurysm rupture. Women with such cerebral metastasis may present with headaches, seizures, and gradually progressive deficits[6]. According to the prognostic scoring system by the WHO, our patient had a prognostic score of 8, which is characterised as high-risk and predicts potential resistance to chemotherapy. The patient was assessed to be of stage 4 in FIGO staging (International Federation of Gynaecologists and Obstetricians). All patients with stage 4 should be treated with intensive combination chemotherapy and radiotherapy[7]. About 78% of patients with stage 4 disease achieve remission[8]. If diagnosis of cerebral metastasis is being made, then whole brain irradiation 3,000 cGy (centi gray units) in 10 fractions can be instituted. Combined chemotherapy with EMA-CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine) is generally well tolerated.

Conclusion

The authors want to emphasise that metastatic choriocarcinoma should be considered as one of the differential diagnosis in women of child-bearing age with intra-cerebral haemorrhages (ICH) and earlier recognition may help in reducing morbidity and mortality due to the high rate of remission of choriocarcinoma, which makes it all the more important to diagnose and initiate treatment at a very early stage.

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CASE REPORT

JIACM 2013; 14(2): 166-8

Lymphocytic hypophysitis: A rare presentation

SH Talib, P Mishrikotkar**, M Naik***, AR Tapadia****, AM Inamdar*****

Abstract

This is a case of autoimmune polyglandular syndrome, type II with lymphocytic hypophysitis (LYH) of autoimmune pathogenesis in a 23-year-old boy, who presented with hypotension and bouts of hypoglycaemia. The patient was noted to have multiple endocrine involvement like thyroid, pancreas, adrenals besides pituitary gland. Presentation of the disease in a male patient, as in this case report, is even more uncommon, and for this reason it merits reporting.

Key words: Autoimmune polyglandular syndrome type II, lymphocytic hypophysitis.

Introduction

We are reporting a case of autoimmune polyglandular syndrome (APS), type II with lymphocytic hypophysitis (LYH) in a 23-year-old boy. LH is an uncommon autoimmune disease in which the pituitary gland is infiltrated by lymphocytes, plasma cells, and macrophages, and its function is usually impaired. Since the first description by Goudie and Pinkerton in 1962[1], about 400 cases have been reported in world literature of which 16 cases are from India with only two cases being male patients[2]. The estimated incidence of AH is one in nine million per year[3].

Case report

A 23-year-old male was hospitalised with problems of intermittent vomiting, headache, loss of weight, and diplopia since 4 years. One month prior to hospitalisation, the patient was hospitalised in Pune with the said problems. The investigations done then revealed his blood counts, haemoglobin, sugar levels, electrolytes, and liver function tests to be normal. Imaging study of MRI brain without contrast was within normal limits with pituitary fossa reported to be normal. Gastroscopy was normal and the patient was discharged as a case of acid peptic disease and was advised to continue H_2-blockers. One month later, he was hospitalised in our institute with vomiting and headache. General examination at time of diagnosis was normal. Axillary and pubic hair, and genitalia were normal. Few hours after hospitalisation, the patient developed convulsions and disorientation. There was no history of sweating, perspiration, and neurological deficit except minimal right-sided facial palsy, with no evidence of bleeding diathesis. His pulse was 100/min regular, blood pressure was 80/60 mmHg, respiration quiet with no signs of failure. The blood sugar

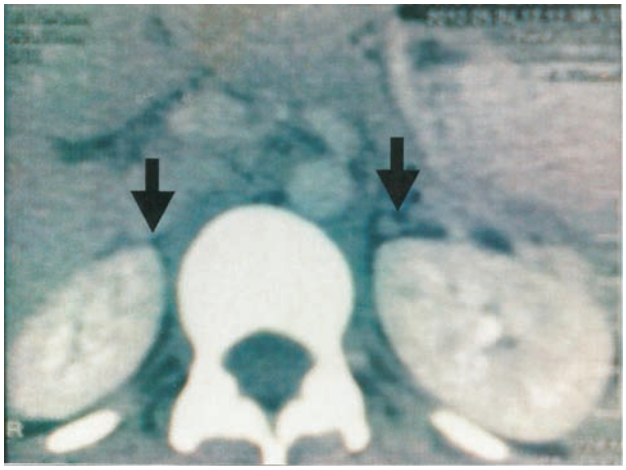

Fig. 1: *MRI of abdomen showing bilateral atrophic adrenal glands.*

(random) estimated was 32mg/dl with blood counts and electrolytes to be within normal range. His ECG showed sinus rhythm. Fundus examination was normal. As the patient had persistent unexplained hypotension and hypoglycaemia for next two days, possibility of Addisions disease was entertained. The basal serum cortisol level estimated next morning was 1.72 ug/dl and post-ACTH test after 60 minutes was 2ug/dl (N: > 20 µg/dl). His serum TSH was 6.66 UI/ml (0.35 - 5.5) and T3 and T4 were 0.71ng/ml (0.8 - 2) and 7.60 µg/dl (4.8 - 11.8) respectively with anti-TPO antibodies > 1,300U/ml (N: < 60). MRI of abdomen for adrenal glands revealed bilateral atrophic adrenals. There was no evidence of mucocutaneous candidiasis.In view of adrenal and thyroid affection, a provisional diagnosis of autoimmune polyglandular syndrome type II was suspected. Further endocrine-related investigations were carried out. His serum testostrerone was 587.22 (N: 241-827) ng/dl, serum ACTH 5.38 (N: 8-25) ng/l, serum prolactin 29.45 (N: 2.10- 17.7) ng/ml, serum insulin 0.16 (N: 1.70-31) mU/l, serum ACE-

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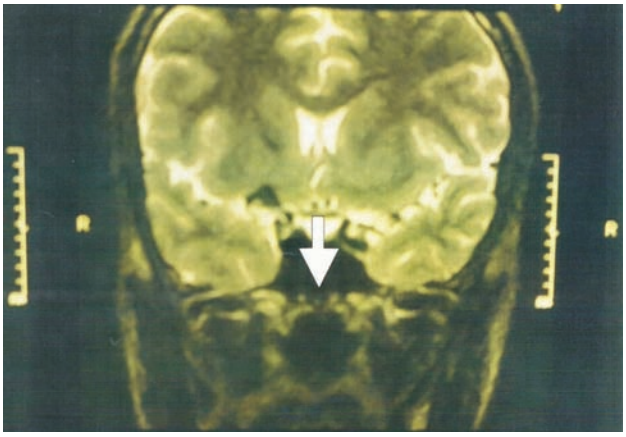

Fig. 2: *MRI of brain with gadolinium showing atrophic pituitary gland.*

32 (N: 8-65) U/l and serum vitamin B12 levels-552 (N 211-911) pg/ml. His MRI brain with gadolinium contrast for pituitary was done which showed atrophic pituitary gland. In view of low ACTH levels, low basal cortisol level, lack of rise of cortisol post-ACTH test, hyperprolactinaemia, bilateral atrophic adrenal glands , atrophic pituitary gland and symptoms of headache, vomiting, diplopia and weight loss, clinical diagnosis of lymphocytic hypophysitis was made. As the patient was found to have, besides these features, involvement of pancreas, thyroid, adrenals, and pituitary gland as revealed from biochemical and imaging investigations, the possibility of APS type II with LH of autoimmune pathogenesis was entertained and the patient was put on hydrocortisone 20 mg in morning and 10 mg in evening. Two months later, the dose was reduced to 10 mg, 5 mg and 5 mg in morning, afternoon, and evening respectively. The patient has had no further episodic hypoglycaemia, headache, vomiting, or blurring of vision for past 8 months. His repeat MRI brain with gadolinium contrast for pituitary is now reported to be normal.

Discussion

The combination of autoimmune adrenal insufficiency with autoimmune thyroid disease and/or type 1 autoimmune diabetes mellitus defines autoimmune polyglandular syndrome, type II. These patients often present with fatigue, weakness, anorexia, nausea, vomiting, abdominal pain, salt craving, diarrhoea, constipation, syncope, weight loss, cutaneous and mucosal pigmentation, hypotension, hypoglycaemia[4]. Our patient presented with most of the above-cited features except diabetes. Conditions associated in patients with autoimmune polyglandular syndrome, type II include autoimmune adrenal insufficiency (100%), autoimmune thyroid disease (69 to 82%), type 1 autoimmune diabetes mellitus (30 to 52%), vitiligo (4.5 to 11.0 %), chronic atrophic gastritis, with or without pernicious anemia (4.5 to 11.0%), hypergonadotropic hypogonadism (4 to 9%), chronic autoimmune hepatitis (4%), alopecia (1 to 4%), hypophysitis (< 1%), myasthenia gravis (< 1%), rheumatoid arthritis (< 1%), Sjögren's syndrome (< 1%), thrombocytic purpura (< 1 %)[4]. Diagnosis of APS type II includes decreased sodium, bicarbonate, and chloride levels, decreased basal levels of cortisol, no increase after ACTH or cosyntropin (Cortrosyn) administration, decreased basal levels of aldosterone and adrenal cortex antibodies or 21-hydroxylase antibodies are virtually always present with thyroid peroxidase autoantibodies (80 to 90 per cent of patients) and thyroglobulin autoantibodies (60 to 70 per cent of patients) detected in patients with Hashimoto's thyroiditis. The present patient had decresed basal cortisol levels with no increase of cortisol after ACTH administration, decreased basal levels of ACTH, and anti-TPO antibodies conforming with APS type II. We had extended our investigations further as the clinical, imaging, and biochemical values obtained were in consistence with the possibility of LH.

Lymphocytic hypophysitis is an autosomal dominant trait with incomplete penetrance, associated with HLA DR3 and HLA DR4. LH is characterised by autoimmune pathogenesis with focal or diffuse inflammatory infiltration and varying degrees of pituitary gland destruction. It typically follows a course in which the pituitary gland initially increases in size simulating a mass, later followed by shrinkage due to fibrotic changes[5,6]. An exhaustive review of the literature shows that women are affected more frequently than men with a ratio of about 5- 8:1[7,8].

At the onset of lymphositic hypophysitis, patients present with symptoms and signs of extrasellar pituitary enlargement and only later do features of hypopituitarism become apparent. Signs and symptoms include headache (60%), visual field impairment (40%), diplopia, hyperprolactinaemia (30%), subclinical hypopituitarism (25%), ACTH deficiency (which is the earliest and most frequent isolated pituitary deficiency seen in 65 % of cases)[9], hypogonadotrophic hypogonadism (usually diagnosed only in males), and isolated GH deficiency[10]. Hyperprolactinaemia affects approximately one-third of patients, causing amenorrhoea/galactorrhoea in women[11] and sexual dysfunction in men[12]. Although antibodies to a 49-kd cytosolic protein, 68 and 43-kd human pituitary membrane antigens are high, they are detected in 70% of patients with histologically confirmed lymphocytic hypophysitis and in 10% of control subjects[13].

Biopsy is the only accurate means of diagnosis but many cases have been managed solely on MRI imaging. MRI

has considerably improved the diagnostic accuracy of LYH by differentiating it from pituitary tumours[14,15,16]. Gutenberg *et al* reported stalk thickening in 79% of the cases[17] though some cases of AH may develop empty sella during the course of the disease as noted in our case. Although histopathology is required for a definitive diagnosis, many cases have been managed solely on clinical grounds[18]. Our patient had presented with headache, vomiting, weight loss, diplopia, decresed basal cortisol levels with no increase after ACTH administration, decreased basal levels of ACTH, elevated anti-TPO antibodies, bilateral atrophic adrenal and atrophic pituitary and therefore clinical diagnosis of LYH was made. To the best of our knowledge there have been only two cases of APS type II with LH of autoimmune pathogenesis reported in male patients in India. Kumar *et al* reported the first case of a 15-year-old boy with elevated anti-TPO antibodies, low basal serum cortisol levels, and negative ACTH test with hypothyroidism and diabetes mellitus[19]. The second case was that of a 43-year-old male whose diagnosed was established solely on pituitary stalk thickening with autoimmune thyroiditis[2].The present case has a complete florid picture of autoimmune polyglandular syndrome associated with abnormal imaging and hormonal assays.

Management of lymphocytic hypophysitis is also a matter of dispute. Corticosteroids have been shown to be beneficial[20,21,22]. Glucocorticoids or other anti-inflammatory and immunosuppressive (methotrexate, cyclosporin A) drugs have been suggested as medical treatment but their long-term efficacy still needs to be confirmed. High-dose methylprednisolone pulse therapy seems to be effective in about 30% of treated patients[22]. Surgical transsphenoidal treatment, is required in patients with symptoms and/or signs of severe compression[23,24].

The follow-up studies in our case with hydrocortisone therapy revealed normal MRI brain and improved hormonal essays. We humbly claim that there is paucity of reported incidences in literature of autoimmune polyglandular syndrome, type II with lymphocytic hypophysitis of autoimmune basis in male patients. Ours is perhaps the third reported case in Indian literature.

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CASE REPORT

JIACM 2013; 14(2): 169-70

Hepatitis B presenting as primary thrombocytopenia and leucopenia without evidence of cirrhosis

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Abstract

Thrombocytopenia and leucopenia is present in advanced cases of chronic hepatitis due to peripheral destruction in an enlarged spleen. This case presented with thrombocytopenia and leucopenia in the absence of that in replicative phase of Hepatitis B. Although rare, hepatitis B should be considered in a case of unexplained thrombocytopenia and leucopenia. The cause is probably autoimmune, but corticosteroid treatment is not indicated. Antiviral treatment takes care the thrombocytopenia and leucopenia.

Key words: Hepatitis B, thrombocytopenia, leucopenia, autoimmune.

Introduction

Extrahepatic haematologic manifestations are commonly observed in cases of Hepatitis B with portal hypertension and splenomegaly, which can cause thrombocytopenia, leucopenia, and anaemia due to peripheral destruction of blood cells. Viral hepatitis B and C may be associated with bone marrow suppression and can cause pancytopenia. If the bone marrow study is normal, the cause may be autoimmune; or infection of blood cells with them, virus itself may be the possible mechanism. Thrombocytopenia can lead to bleeding and thus restrict any further invasive procedure. Leucopenia can lead to sepsis. Corticosteroid therapy is not indicated due to its immunosuppressive effect and fear of flare-up of infection. Antiviral therapy improves blood counts gradually if there is no major bleeding threat and sepsis.

Case history

A 47-year-old female, a known case of hypertension on amlodipine, (coronary artery disease - TMT positive) on clopidogrel 75 mg daily, pantoprazple presented in the OPD with purpura and ecchymotic patches on skin since 10 years which used to subside spontaneously. Its frequency and severity had increased since the last few months.

No history of jaundice, ascites, or pedal oedema was present. No history of haematemesis, melaena or menorrhagia was elicited. Her physical examinaton was normal except for ecchymosis and purpura. No signs of organomegaly, ascites, or venous prominence were present. Her CVS, chest, and CNS was clinically normal.

Investigation

Detailed work-up on the lines of bleeding diathesis was done. CBC showed platelet count 8,100/cmm, total leucocyte count was low - 3,280 cells/ml, SGOT was 226 U/l and SGPT - 305 U/l, bilrubin - 0.7mg/dl, APTT - 41 seconds/control - 36 seconds. PT-normal (13.2 seconds/ control 12.1 seconds), INR was 1.1. Manually repeated platelet count was also low - 82,000/cmm. Hb - 12.9 gm/ dl and MCV - 94 fl. Peripheral smear examination impression showed normocytic normochromic RBCs with leucopenia (neutropenia) and thrombocytopenia (bicytopenia). TSH was 2.9 μU/ml. USG abdomen was normal (no splenomegaly or hepatomegaly or coarse echotexture of liver) except small calcific foci in right lobe of of liver. Her folic acid and serum vitamin B 12 was normal. Anti-HCV was negative, HIV 1 and 2 was negative. Hepatitis B surface antigen was positive, HbeAg - negative, IgM anti-HBc was negative. HBV DNA count was high - 2,192 IU/ml.

Bone marrow aspiration report showed normal trilineage haematopoiesis, no increase in the number of blasts, no evidence of peripheral destruction of platelets, no evidence of infiltration in bone marrow, and megakaryocytes seen in adequate in numbers. Bone marrow biopsy showed normal trilineage haematopoiesis. Her ANA and dsDNA was done to rule-out SLE which was negative. Endoscopy of upper GIT showed antral gastritis only. The patient received *H. pylori* eradication course to rule-out *H. pylori* related immune thrombocytopenia.

After the *H. pylori* eradication course with a three drugs regimens for 14 days, her platelet count did not improve.

Based on the above history, clinical findings, laboratory diagnosis and virological markers, she was diagnosed as a case of chronic active hepatitis B without cirrhosis, complicated by immune thrombocytopenia and leucopenia.

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Discussion

Extrahepatic features of chronic hepaitis B reflect immune-complex phenomena such as vasculitis, immune complex nephritis, arthritis, a serum-sickness-like illness, and polyarteritis nodosa[1]. Immune thrombocytopenia and leucopenia are rarely associated with hepatitis B. It is more commonly associated with hepatitis C virus infection. Infection with hepatitis B virus should be kept in mind in patients presenting with leucopenia and thrombocytopenia. Corticosteroids are not indicated in the treatment of thrombocytopenia in hepatitis B infection[2,3,4] as they may cause flare-up of the viral infection. Patients having severe thrombocytopenia and severe bleeding may respond to intravenous immunoglobulin therapy[5]. Intravenous immunoglobulin has a transient effect; it cannot be curative in the long run. The more recently launched thrombopoietin receptor agonist Eitrombopag 25 - 50 mg daily (Revolade®, GlaxoSmithKline) can improve platelet count but its high cost and non-easy availability leads to its rare usage. GMCSF has been safely used in patients with cirrhosis and leucopenia complicated by sepsis to improve the leucocyte count[6]. This patient was started on Entacavir (Baraclude®) 0.5 mg daily. Her total leukocyte count increased to 3,930/cmm and platelet count increased to 88,000/cmm after one month of therapy. Her bleeding manifestation in skin subsided with no fresh purpura even when platelet count did not improve significantly, which reflects correction of functional abnormality. The patient is under close follow-up for further bleeding manifestation and change in cell counts.

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"Science has 'explained' nothing;
the more we know, the more fantastic the world becomes
and the profounder the surrounding darkness."

– Aldous Huxley: Views of Holland.

CASE REPORT

JIACM 2013; 14(2): 171-2

A rare presentation of 2, 4-Dichlorphenoxyacetic acid (2, 4-D) poisoning

Nitya Nand, Hitender Kumar***

Abstract

2, 4-Dichlorphenoxyacetic acid (2, 4-D) is an agricultural herbicide widely used to kill broad-leaved weeds in wheat cultivation. Most of the reported cases of documented poisoning are from Europe and North America. However, only six cases of poisoning with this compound have been reported from India. We report this case a young adult who ingested it with suicidal intent and developed neurological, cardiac, and respiratory toxicities ultimately leading to death.

Key words: Dichlorphenoxyacetic acid, herbicide, poisoning.

Introduction

2,4-Dichlorphenoxyacetic acid (2,4-D) alkali or amine salts or esters are used as agricultural herbicides against broad-leaf weeds in cereal crops as well as on pastures and lawns, in parks, and on golf courses. It is used extensively in the northern part of India where wheat is mainly cultivated. It can be absorbed via the oral, dermal, and inhalation routes. The toxic and lethal levels of 2, 4-D in human blood and tissues are still not well defined. In general, the acute lethal levels of 2, 4-D in the plasma appear to lie between 447 and 826 mg/litre. Its toxic effects involve heart, central and peripheral nervous system, liver, kidneys, muscles, lungs and endocrine system[1]. It is rarely reported as an agent used for attempting suicide. Most of the reported cases of documented poisoning due to 2, 4-D are from Europe and North America[2, 3]. To the best of our knowledge, six cases of documented poisoning with this compound have been reported from India[4, 5].

Case report

A 19-year-young male was admitted with alleged history of ingestion of about 50ml of 2, 4-Dichlorphenoxyacetic acid (2, 4-D) solution with suicidal intent. He became markedly restless and drowsy two hours after the ingestion of this poison. He then had multiple episodes of vomiting without any blood. Patient was given gastric lavage, injection atropine 6mg, and intravenous fluids outside this institute and was then referred to this hospital. On physical examination, he was restless and drowsy and haemodynamically stable. Blood pressure was 128/84 mmHg and the pulse was 144/min, regular, and of good volume. He was tachypnoeic with respiratory rate of 32/min. His pupils were dilated and showed sluggish reaction to light. Diffuse ulceration was noticed in the oral cavity along with brownish discoloration of the lips. There was no icterus, no cyanosis, and neck veins were not distended. The chest had bilateral vesicular breathing; abdomen was soft and without any organomegaly. On cardiac auscultation, the first and second heart sounds were normal in intensity without any audible murmur. Complete haemogram showed haemoglobin of 13.5 gm/dl, TLC - 7,800; and DLC revealed P74, L22, M2, E2. Platelets were normal (1,97,000/mm^3). Biochemical parameters showed bilirubin 0.8 mg/dl, SGOT - 73 IU (normal: 20 - 40), SGPT - 43 IU (normal: 20 - 40), alkaline phosphatase - 231 IU, amylase 88 IU (normal: 0 - 82), Na^+-140 meq/l, K^+-4.9 meq/l, urea-26-mg/dl, creatinine-1.1 mg/dl. Arterial blood gas analysis revealed PaO_2 - 70.3, $PaCO_2$ - 19, pH - 7.475, HCO_3 - 13.5, O_2 sat - 95.6%. Electrocardiogram revealed sinus tachycardia with heart rate of 144/min. Urine complete examination and chest x-ray were normal. He was treated with intravenous fluids and antibiotics for suspected aspiration pneumonia. However, his sensorium continued to deteriorate and he developed respiratory depression for which he was intubated and managed with mechanical ventilation. He continued to deteriorate despite supportive measures and died on the next day following a cardiac arrest.

Discussion

2, 4-Dichlorphenoxyacetic acid (2, 4-D) compounds are widely used as agricultural herbicides against broad-leaf weeds in cereal crops as well as on pastures and lawns, in parks, and on golf courses. The common formulations are either solid alkali salt concentrate, salt miscible solution, or as ester-based emulsifiable concentrate[1]. Although it has been available as a herbicide for many years, there are few reported cases of occupational exposure and its use as a suicidal agent[2-5]. It can be absorbed via the oral, dermal, and inhalation routes. The toxic and lethal levels of 2, 4-D in human blood and tissues are still not well

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defined. In general, the acute lethal levels of 2, 4-D in the plasma appear to lie between 447 and 826 mg/litre. Blood levels of 2, 4-D can be measured most accurately with gas-liquid chromatography with electron-capture detection (GLC-EC)[1]. Nausea, vomiting, abdominal pain, diarrhoea and, occasionally, gastrointestinal haemorrhage are the early effects following ingestion of these compounds. Hypotension, which is common, is due predominantly to intravascular volume loss, although vasodilatation and direct myocardial toxicity may also contribute. Its toxic effects involve heart, central and peripheral nervous system, liver, kidneys, muscles, lungs, and endocrine system. It also produces haematological and biochemical disturbances. Mechanisms of toxicity including dose-dependent cell membrane damage, uncoupling of oxidative phosphorylation and disruption of acetyl-coenzyme A (acetyl-CoA) metabolism[3].

The initial clinical manifestations of 2, 4-D poisoning are very similar to poisoning with anticholinesterase compounds, making it even more difficult for the treating physician to suspect poisoning due to these compounds. Our patient was also treated as a case of anticholinesterase poisoning by a private practitioner and was given injection atropine. Our patient developed respiratory distress either due to CNS depression or due to respiratory muscle paralysis and was put on mechanical ventilation. Muscle involvement occurs in the form of muscle fibrillation, myotonia, loss of reflexes, and muscular weakness. Skeletal muscle damage results in increased levels of creatine kinase and myoglobinuria which, in turn, leads to renal failure. But in our patient, there was no evidence suggestive of myotoxicity and renal failure. Metabolic acidosis, increased aminotransferase activity, pyrexia, and hyperventilation have also been reported[3].

The reported neurological effects are impaired coordination, unconsciousness, and coma. Unconsciousness or coma may result from a direct CNS depressant action or a number of metabolic derangements in these patients. Hypertonia, hyperreflexia, ataxia, nystagmus, miosis, hallucinations, convulsions, fasciculation, and paralysis may present at variable intervals during the course of systemic toxicity. Our patient developed respiratory distress which was attributed to respiratory muscle involvement.

There is no specific antidote available for 2, 4-D poisoning. Management is supportive in the form of maintaining hydration, assisting respiration, and preventing arrhythmias and aspiration. Since myoglobinuria produces nephrotoxicity, alkaline diuresis may be helpful in preventing renal damage[6]. Urine alkalinisation with high-flow urine output may possibly enhance herbicide elimination and should be considered in all seriously ill patients. Although the exact mechanism is not clear, haemodialysis may also help by eliminating the 2, 4-D[7].

To conclude, 2, 4-D is a rare agent used for attempting suicide. Initial manifestations with 2, 4-D poisoning are similar to anticholinesterase poisoning. The early recognition of signs of corrosive injury, tachycardia, muscle weakness, and CNS toxicity will help identify cases with 2, 4-D poisoning and guide the physician for proper management of these cases.

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"Medicine is a science of uncertainty, and an art of probabilities."

– Sir William Osler (1849-1919).

CASE REPORT

JIACM 2013; 14(2): 173-4

Cardiac involvement in Henoch-Schönlein purpura

Deepak Sundriyal, BB Gupta**, Brijesh Sharma***, MPS Chawla****

Abstract

Cardiac involvement in Henöch-Schonlein purpura (HSP) is rare with only a few case reports available in the literature . We report a 21-year-old male who presented with rash, arthralgia, and chest pain. Raised cardiac enzymes indicated myocardial injury. There was evidence of pericarditis on echocardiography. The patient was diagnosed as having Henoch-Schönlein purpura with cardiac involvement.

Key words: Henöch-Schonlein purpura, vasculitis, rash.

Introduction

Henoch-Schönlein purpura is a systemic vasculitis characterised by nonthrombocytopenic purpura, abdominal pain, arthritis, and sometimes intestinal haemorrhage and renal involvement. Cardiac involvement is an uncommon manifestation of the disease. A case of Henoch-Schönlein purpura with cardiac involvement is reported here.

Case report

A 21-year-old male student, resident of Kanpur, Uttar Pradesh, presented with complaints of fever and an episode of non-exertional chest pain 2 days prior to admission. He also complained of decreased urine output, joint pains and rashes over the lower extremities for the last 2 days. There was no history of headache, vomiting, neck pain, altered sensorium, sore throat, insect bite, drug intake or any bleeding manifestations. Past history and family history were unremarkable.

On examination, the patient was conscious and oriented. His blood pressure was 148/94 mmHg in the right arm in supine position with no appreciable difference in all four limbs. All peripheral pulses were palpable. Purple palpable rash was present over the extremities up to the thighs and elbows (Fig. 1). Bilateral elbow, wrist, knee, and ankle joints were swollen and tender. Movements at the joints were restricted. Systemic examination was normal.

Investigations revealed a haemoglobin of 11.7 gm/dl, total leucocyte count of 20,000/cumm with neutrophilia and normal platelet counts. Blood urea was 125 mg%; serum creatinine was 3.7 mg % and urine examination revealed granular casts and albuminuria. 24-hour urine protein estimation was 2.1 grams.

Liver function tests and serum electrolytes were within normal range. Anti-streptolysin O (ASLO), anti-nuclear antibody (ANA), and anti-neutrophilic cytoplasmic antibody (ANCA) titres were not raised. Markers for hepatitis B and C infections were negative.

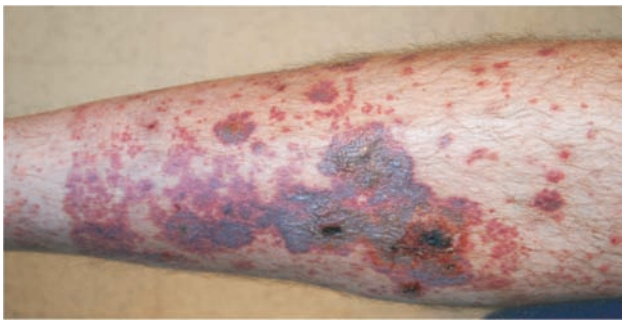

Fig. 1: *Palpable purpura on leg.*

ECG at admission was suggestive of ST elevation in leads I, II, aVL, aVF, V5 and V6 (Fig. 2). Subsequent ECGs were normal. Cardiac enzymes were raised. Troponin T was 2.85 ng/ml (normal: < 0.1 ng/ml) and CPK-MB was 44.00 U/l (normal: 0.10-4.94 U/l).

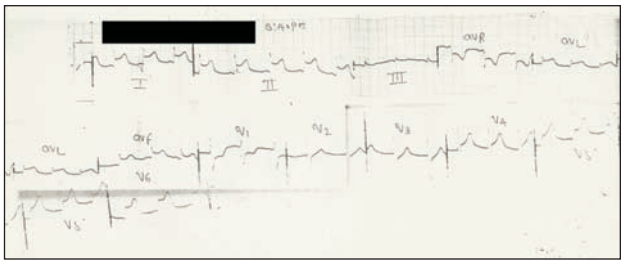

Fig. 2: *ECG from same patient showing diffuse ST segment elevation.*

2D-echocardiography was suggestive of moderate pericardial effusion. Skin biopsy from the site of rash revealed leucocytoclasis with fibrinoid necrosis of vessels, consistent with leucocytoclastic vasculitis (Fig. 3).

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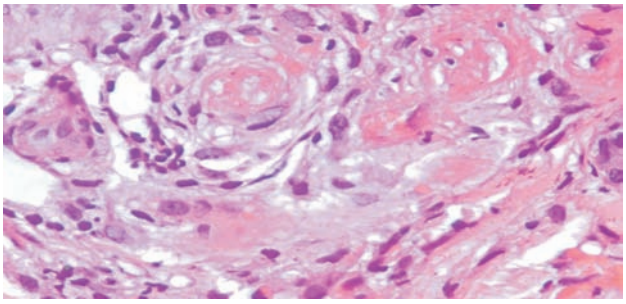

Fig. 3: *Skin biopsy from the rash showing leucocytoclasis and fibrinoid necrosis suggestive of leucocytoclastic vasculitis. H & E, 40 x 10.*

Discussion

The American College of Rheumatology criteria for HSP (sensitivity 87.1%, specificity 87.7%) require the presence of at least two of the following: (1) Age $\leq$ 20 years at disease onset; (2) Palpable purpura; (3) Acute abdominal pain; (4) Biopsy showing granulocytes in the walls of small arterioles/venules[1]. The EULAR/Pre S criteria require a mandatory criterion of palpable purpura with lower limb predominance, plus at least one of the following criteria: (1) diffuse abdominal pain; (2) IgA deposition in any biopsy; (3) Arthritis/arthralgia; (4) Renal involvement (haematuria and/or proteinuria)[2].

Reported incidence of HSP in adult population is 3.4 to 14.3 cases per million[3]. HSP predominantly affects the skin, joints, gastro-intestinal tract, and kidneys. Unusual presentations can be in the form of central nervous system involvement as seizures, or pulmonary involvement as tracheo-bronchitis or interstitial pneumonitis[4,5]. Cardiac involvement is very uncommon with documented involvement in HSP being limited to only a handful of case reports in the literature. Cardiac involvement can occur in the form of chest pain, bradycardia, and hypotension. Coronary events in the form of T wave inversions and myocardial infarction have been described[6,7]. Bundle branch block and subendocardial leucocytoclastic vasculitis have been reported. Pericarditis and subsequent pericardial effusion is still very unusual in Henoch-Schnölein purpura[8].

Most patients of HSP recover completely and some do not require therapy. Therapy is not well established and glucocorticoids may be of help in severe cases of tissue oedema, arthralgias, and abdominal discomfort. Patients of glomerulonephritis may benefit from plasma exchange combined with cytotoxic drugs.

Our patient presented with purpura, arthritis, kidney involvement, and skin biopsy features of leucocytoclastic vasculitis, and thus satisfied both ACR as well as EULAR/Pre S criteria for HSP. He also had cardiac involvement in the form of diffuse ST segment elevation (subsequent ECGs being normal) with markedly raised cardiac enzymes and echocardiographic evidence of pericarditis and effusion.

The patient was managed conservatively with NSAIDs and intravenous fluids, and his condition improved progressively. Prednisolone was given in the doses of 1 mg/kg/day for 7 days. Joint pain and rash subsided and urine output normalised in due course of time. His subsequent ECGs were normal.

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"How unfair! Only one health, and so many diseases."

– Victor Schlichter.

CASE REPORT

JIACM 2013; 14(2): 175-8

Blue rubber bleb naevus syndrome producing recurrent anaemia and asthenia

Ashis K Saha, Arup K Kundu***

Abstract

Blue rubber bleb naevus syndrome (BRBNS) is a rare congenital angiomatosis principally due to involvement of two systems, i.e., skin and gastrointestinal system, with venous malformations, which may lead to acute or chronic gastrointestinal bleeding resulting in chronic and refractory iron deficiency anaemia though other systems may also be involved. Here we present such a case in an aged Muslim female who presented with anaemia, positive occult blood in stool, and bluish maculo-papular lesions on the tongue, neck, palm, and oesophageal mucosa.

Key words: Blue rubber bleb naevus syndrome, Bean syndrome, anaemia, vascular malformation, upper GI endoscopy.

Introduction

Blue rubber bleb naevus syndrome (BRBNS) is essentially characterised by cutaneous and gastrointestinal haemangioma, though it may involve all the systems of the body from head to feet, i.e., central nervous system, eyes, nasal cavity, nasopharynx, thyroid, bones, muscles, pleura, pericardium, peritoneum, synovium, lung, liver, spleen, kidney, penis, vulva, and bladder[1,2]. There may be pressure effects of venous malformations resulting in bony deformities. It can present as sporadic cases but the autosomal mode of inheritance has been fully recognised. This disease was first recognised by Gascoyen in 1860 and later on in the year 1958, William Bean distinguished these 'blue rubber bleb' lesions from other vascular lesions of the skin and hence the condition is also known as 'Bean syndrome'[3]. The actual cause of this condition is still unknown. BRBNS may present with chronic anemia and asthenia due to very slow oozing of blood from the gastrointestinal mucosa to massive life threatening bleeding.

Case report

A 62-year-old Muslim female from a remote village of the Sundarbans, South 24 Parganas (West Bengal), came to our out-patient department with asthenia, fatiguability, and pallor. She had past history of recurrent anaemia for last 15 years for which she received treatment with intravenous proton-pump inhibitors (PPI) and blood transfusion in a primary health centre in Sundarbans, without any history of massive bleeding. Upper GI endoscopy was advised to the patient, but she as well as her family members refused the investigation. Neither had she any history of nausea, vomiting, haematemesis, melaena, haematochezia, abdominal pain; nor there was any history of analgesic abuse. None of the family members suffered from chronic anaemia like her and she was not born of a consanguineous marriage.

On examination, she was moderately anaemic with a thin build. The vitals were within normal limits. There were multiple maculo-papular rubbery blebs seen on the right palm (Fig. 1), dorsum of the tongue (Fig. 2), and face

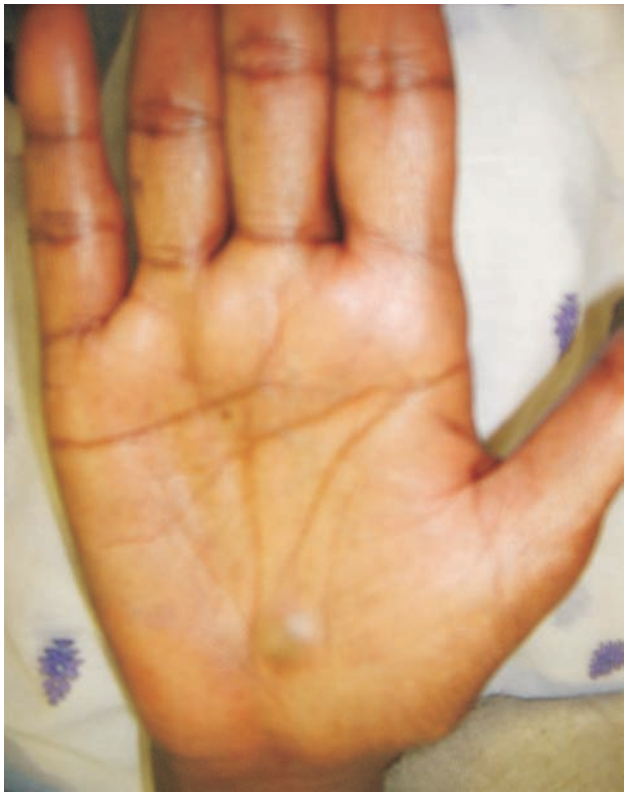

Fig. 1: *Bluish rubbery naevi over the right palm.*

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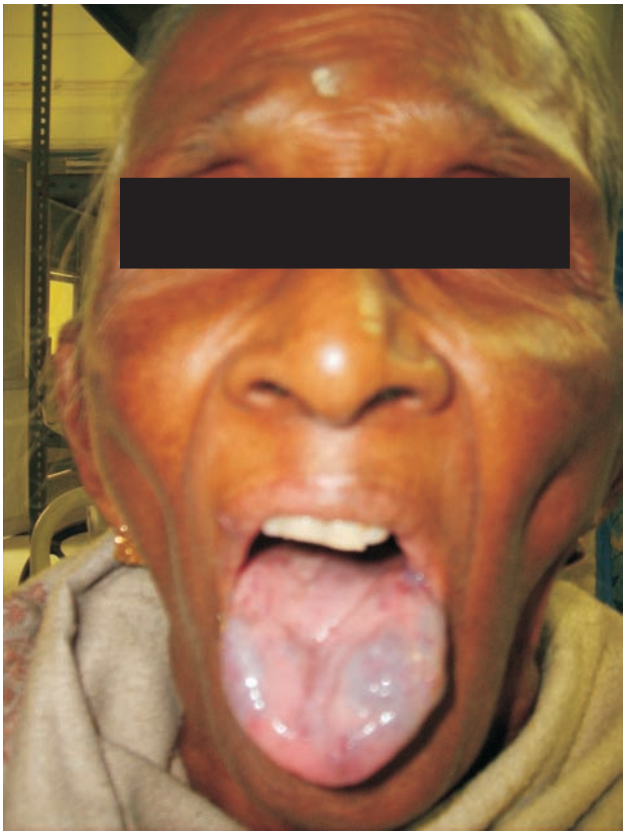

Fig. 2: *Multiple bluish rubbery naevi over the tongue.*

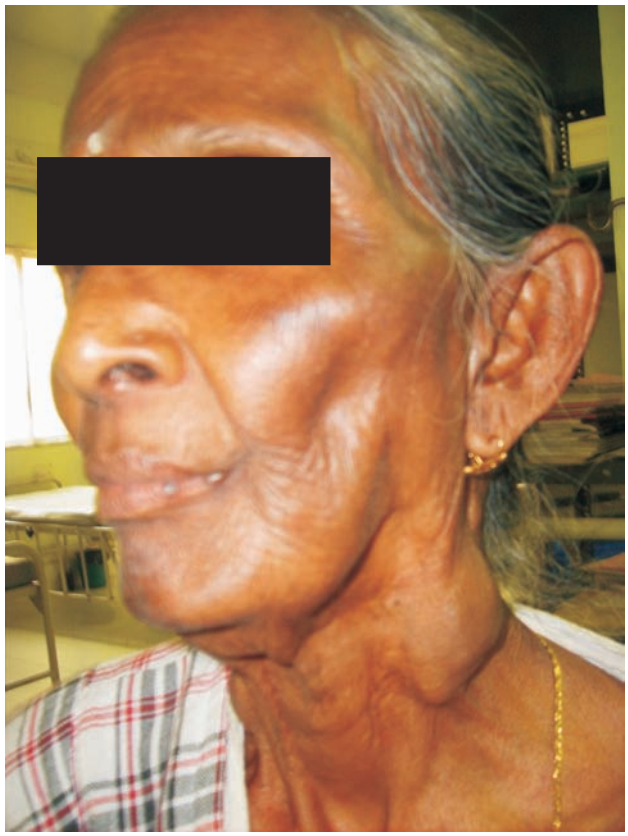

Fig. 3: *Rubbery naevi on the left side of neck over external jugular vein.*

ranging from 2 mm to 1 cm diameter in size. A large boggy swelling was seen in the line of left external jugular vein (Fig. 3). On the dorsal surface of the tongue, there were two large bluish blebs measuring 1.0 cm each in diameter, and several other smaller blebs measuring < 2 mm in diameter. All the lesions were compressible, non-tender, soft, and smooth-topped. No evidence of bleeding spot was seen in any of the lesions. These lesions were present since childhood but did not produce any symptom compelling the patient to seek medical or surgical help. But according to her statement, these lesions were gradually but very slowly increasing in size since the last couple of months. Despite meticulous search, there was no palpable lymphadenopathy or organomegaly. Examination of other systems were normal.

A complete haemogram revealed features suggestive of iron deficiency anaemia with the following findings: Hb-8.5 g/dl; TLC - 9,100/cumm N - 68, L - 27, M - 4, E - 1, PCV - 25%; MCV - 73 fl; MCH - 23 pg/cell; MCHC - 27.10 g/dl; platelet count - 3,17,000/cumm, reticulocyte count - 3.5%; mean ESR - 46 mm/hr; aniso - poikilocytosis and microcytic-hypochromic anaemia. Serum iron was 40 µg/dl, serum ferritin - 30 ng/ml, TIBC - 350 µg/dl, and transferrin saturation was 12%. Haemoglobin electrophoresis was essentially normal. Clotting time, bleeding time, prothrombin time and activated partial thromboplastin (APTT) time were within normal limits. Liver function tests, serum electrolytes, urea, creatinine, and plasma glucose levels showed no abnormality. Stool was positive for occult blood on 3 consecutive days. Routine examination of urine showed no abnormality. USG of the whole abdomen and chest X-ray were normal.

Biochemical examination revealed liver function tests, renal parameters, serum electrolytes to be within normal limits. Upper gastrointestinal (GI) endoscopy revealed multiple (4 in number) bluish papular blebs or elevated naevi, measuring 2 mm to 1 cm in diameter seen in the upper and lower oesophageal mucosa (Fig. 4 and 5); but there was no evidence of any oozing lesion in the oesophagus. No such lesion was seen in the stomach and duodenal mucosa. Colonoscopy was essentially normal.

Primary impression on the basis of dermatological and gastrointestinal mucosal lesions was "blue rubber bleb naevus syndrome (BRBNS)".

Histological examination of biopsy specimen of one lesion on the palm revealed ectatic venous channels with flat endothelium and deficient smooth muscle, filled with a

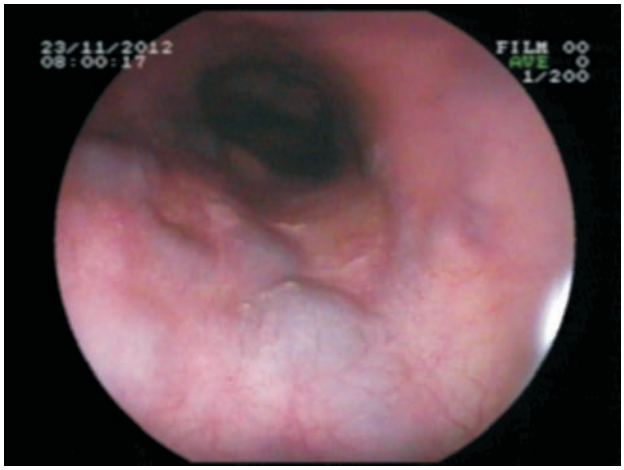

Fig. 4: *Elevated bluish naevi in the lower end of the oesophagus.*

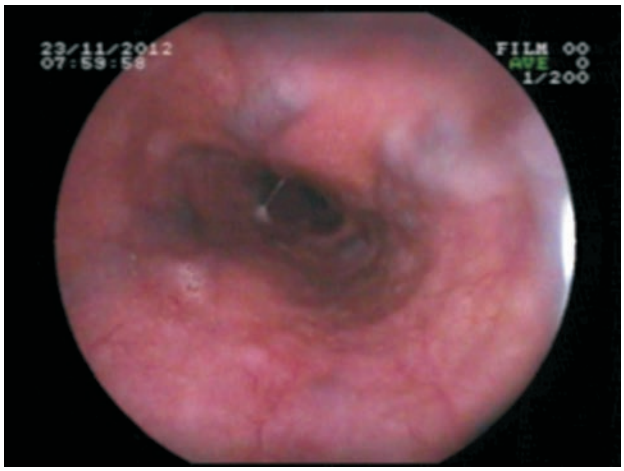

Fig. 5: *Two large naevi seen in oesophagus without any oozing of blood.*

blood clot. The histology is compatible with the diagnosis of BRBNS.

A diagnosis of BRBNS was made on the basis of history of gradually increasing size of bluish, compressible, discrete blebs on the palm and dorsal surface of tongue, with similar lesions in the upper and lower oesophageal mucosa seen on upper gastrointestinal endoscopy along with histological picture of ectatic venous channels on skin biopsy.

Discussion

Blue rubber bleb naevus syndrome is a rare congenital disorder of venous malformation as evidenced in skin and gastrointestinal mucosa or any other organ in the body. Less than 200 cases are described in world literature, proving its rarity[3]. The inheritance of this syndrome is autosomal dominant, though most cases seem to be sporadic; the actual aetiology is unknown. The skin lesions are generally non tender, macular, or maculopapular bluish black or blue blebs of varying sizes ranging from 2 mm to 5 cm in diameter. These lesions are of three types[4]: 1) blue rubbery compressible blebs having wrinkled surface, becoming empty on giving gentle pressure and refilling on releasing the pressure, 2) large cavernous blebs compressing adjacent structures, 3) blue macular areas distributed all over the skin of the body, but mainly on the palms, soles, and trunk. This syndrome has been reported in all races, but Caucasians appear to be mainly affected; sex distribution is almost equal. Lesions in the GI tract occur anywhere from oral to anal mucosa. In contrast to the skin lesion, the gastrointestinal lesion frequently bleeds. Patient with blue bleb in GI tract may also present with intussusception and volvulus. The patient may present with chronic iron deficiency anaemia, asthenia, with positive occult blood test of stool. This suggests the importance of upper GI endoscopy in patients presenting with anaemia and typical skin lesions. These type of patients also require regular surveillance and follow-up in future.

In this case, the differential diagnoses include the following: Hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease), Maffucci syndrome, Klippel-Trenaunay-Weber syndrome, Parkes Weber syndrome, and Peutz-Jeghers syndrome. Hereditary haemorrhagic telangiectasia, an autosomal dominant disease, is characterised by cherry red telangiectatic millet seed-like lesions in the skin[5], lips, nasopharyngeal mucosa, oral mucosa, tongue, with histological involvement of capillaries and venules which differentiates this condition from BRBNS. Maffucci syndrome is diagnosed by benign enlargement of cartilage (enchondroma), bony deformities, dark haemangioma, which is absent in BRBNS. Klippel-Trenaunay-Weber syndrome is characterised by vascular naevus in lower limb, varicose veins limited to the affected side, and lesions appearing after birth or in childhood, hypertrophy of all tissues of the involved limb – mainly bones: GI tract involvement is rare, but if present, the patient commonly presents with haematochezia. Peutz-Jeghers syndrome has intestinal polyposis which is totally different from the vascular lesions of BRBNS.

The treatment of GI lesions is principally symptomatic and supportive with blood transfusion, iron supplementation, and PPI (proton pump inhibitor). Interferon, octreotide, and corticosteroids are not helpful to stop intestinal bleeding. Variceal sclerotherapy provides mixed results. Surgical therapy is not at all indicated. Skin lesions rarely require treatment (laser therapy) except for cosmetic purposes.

Conclusion

BRBNS is a rare congenital disorder characterised by typical lesions in skin and gastrointestinal tract, recurrent anaemia and with or without positive occult blood test of stool[3]. It is mandatory to perform upper GI endoscopy, and if possible meticulous search should be done to exclude intracranial vascular malformations. The patient should be counselled about the nature of the disease and the necessity of follow-up.

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CASE REPORT

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Nonketotic hyperglycaemia presenting as myoclonus

P Agrawal, S Sompura**, A Raj*, SC Yadav**

Abstract

A 64-year-old male presented to us with sudden, brief, abrupt, jerky involuntary movements of both upper limbs, referred to as myoclonus. On further work-up, the patient was found to have uncontrolled diabetes with absent ketones. Other causes of myoclonus were excluded, and on MRI of the brain no abnormality was found which could explain these movements. After strict glycaemic control with insulin, these movements disappeared confirming this as a neurological complication of diabetes.Cerebral dysfunction due to hyperglycaemia without hyperosmolarity resulted in these abnormal movements. This article reveals the importance that diabetes should be considered in the differential diagnosis of all neurological conditions as it can affect any part of the nervous system leading to varied clinical presentations such as myoclonus; even this neurological manifestation can present as the first sign/symptom of diabetes. Strict glycaemic control is the only modality of treatment needed in such cases.

Keywords: Nonketotic hyperglycaemia, diabetes, myoclonus.

Introduction

The term myoclonus refers to sudden, brief, shock-like movements. These movements may be "positive" or "negative". Positive myoclonus results in contraction of a muscle or multiple muscles. In asterixis, or negative myoclonus, there is a brief loss of muscle tone and then the tightening (contraction) of other muscles; this results in a flapping-type motion. These movements, which cannot by stopped at will (nonsuppressible), often have a characteristic saw-tooth pattern, and they usually disappear during sleep. Myoclonus can be physiological, familial, progressive myoclonic epilepsy due to lysosomal and glycogen storage disorder, mitrochondrial disorders, secondary due to inborn errors of metabolism, trauma, neurodegenerative disorders, kidney and liver failure, nonketotic hyperglycaemia, hypercapnia, metabolic alkalosis[1-4].

Nonketotic hyperglycaemia manifests as a treatable cause of myoclonus; and proper glycaemic control remains the cornerstone of management in such cases.

Case report

A 62-year-old male came with complaints of sudden, brief, abrupt, involuntary movements confined to both upper limbs, referred as myoclonus, since the last 3 - 4 days. These movements were not associated with unconsciousness, or bowel, bladder involvement. There was no similar family history and also no past history of trauma, seizures, hypertension, alcoholism, smoking, or drug abuse. On examination, higher mental functions were normal, sensory system was intact, nutrition, tone, power, reflexes, and cranial nerve examination were normal. Tests for cerebellar function were normal. Investigations revealed Hb - 13 g/dl, TLC - 5,200/cumm, SGPT - 24U/l, SGOT - 26U/l, Na^{+}/K^{+}- 139/4.1 mmol/l, inorganic Ca^{++}- 1.16 mmol/l, Mg^{++}- 1.9 mmol/l, serum creatinine - 1.0mg/dl, Random blood sugar - 368 mg/dl, serum osmolarity - 287 milliosmoles/l, urine R/M - Alb-trace, sugar - 2+, ketones-nil, pus cells - nil. EEG, MRI brain and spine, chest x-ray, ECG were normal. Arterial blood gas (ABG) analysis was absolutely normal. After glucose tolerance test, the patient was declared to be a diabetic. Blood sugar was controlled with subcutaneous insulin and dietary advise within the next 3 days. Jerky movements decreased in frequency and stopped completely with better glycaemic control. The patient was discharged on subcutaneous insulin and advised to remain in continuous follow-up with blood sugar monitoring.

Discussion

Hyperglycaemia produces a global decrease in regional cerebral blood flow and thus may reduce local amounts of γ-aminobutyric acid (GABA). Decrease of GABA and acetylcholine, the lack of energy and metabolic acidosis have been hypothesised to cause myoclonus associated with nonketotic hyperglycaemia. Also, positron emission tomography (PET) scan studies had shown reduced cerebral glucose metabolism, while hypoperfusion in the affected region was seen on single photon emission computed tomography (SPECT). These findings were interpreted as a local failure in vascular autoregulation in the setting of pre-existing microangiopathic disease and recurrent metabolic derangements. In addition, proton MR spectroscopy studies had showed an increase

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in lactic acid, acetate, lipids, and a decrease in *N*-acetylaspartate and creatine, suggesting the presence of energy depletion and neuronal dysfunction. In the cranial MRI of our case, T1 and T2-weighted scans were normal, there was no other abnormality to explain the involuntary movements. The prognosis of myoclonus associated with nonketotic hyperglycaemia is excellent. The abnormal movements usually disappear with treatment. Blood glucose control is usually sufficient to treat such a case. In our case, the involuntary movements completely disappeared with glycaemic control with insulin[5-7].

Conclusion

Our case indicates that the direct effect of nonketotic hyperglycaemia may cause myoclonus by neuronal dysfunction. The involuntary movements can be corrected with blood glucose control within a short span of time.

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"Better to hunt in the fields, for health unsought
Than fee the doctor for a nauseous draught.
The wise, for cure, on exercise depend;
God never made his work for man to mend."

– John Drydon.

CASE REPORT

JIACM 2013; 14(2): 181-3

Ramipril-induced bullous drug eruptions

P Agrawal, S Sompura**, SC Yadav*, AK Singh**

Abstract

Side-effects like cough, dysgeusia are common with ACE inhibitors, but skin rash like bullous drug eruption is rare, especially with ramipril. Here we are reporting a case of a 55-year-old female who developed bullous drug eruptions with the first dose of ramipril.

Key words: ACE inhibitors, ramipril, bullous drug eruptions.

Introduction

ACE inhibitors are very frequently used drugs as anti-hypertensives, and as remodelling agents in heart failure, in diabetic nephropathy to prevent its progression and besides this, also for other varied clinical uses. Other than their side-effects on various systems, these agents are known to cause a multitude of dermatological side effects. Skin rash occurs during treatment with captopril in 1 - 6% of cases. While skin rashes, pruritus, and urticaria are quite frequent, other rare clinical events include photosensitivity, onycholysis, various skin eruptions, hyperhidrosis, pemphigus, bullous pemphigoid, lichen planus, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome[1-2].

This case report is mainly focussed on skin-related side effects of ACE inhibitors and also impresses upon clinicians to keep their eyes open on such rare dermatological manifestations while prescribing ACE inhibitors like ramipril which are very frequently used as antihypertensives now-a-days.

Case report

A 55-year-old female developed bullous skin eruptions over both hands upto the wrists with the first dose of ramipril (5 mg) prescribed as an antihypertensive. She had not taken any drug treament before or at the time of developing skin eruptions. She developed a symmetrical palpable bullous eruption over both hands extending up to the wrists (Figs. 1-6). These eruptions did not extend further in the ensuing days. Blood investigations were unrevealing. ESR was within normal range, anti-nuclear antibody test (ANA) was negative. Given the close temporal relationship between the skin eruptions and the first dose of ramipril, it was felt that the skin eruptions could have been caused by ramipril. Therefore ramipril was discontinued and another class of antihypertensive was started. The patient was referred to a dermatologist who, after taking history and local examination, concluded that these were bullous drug eruptions due to ramipril use. The dermatologist started a short course of steroid and these skin lesions resolved completely within a week. The patient was advised not to take ramipril further and was assured that these were drug eruptions which were unlikely to appear again.

Discussion

ACE inhibitors are commonly prescribed drugs and are a standard therapy in the management of hypertension and heart failure. Recognised adverse cutaneous effects include angioedema, bullous eruptions, urticaria, erythema multiforme, and vasculitis. Psoriasiform maculopapular and lichenoid eruptions have also been described. Dermatologic side effects are typically the result of hypersensitivity reactions[3]. Rare cases of pemphigus, including lichen planus pemphigoides, have been associated with the use of ramipril and other ACE inhibitors[5]. In addition, Stevens-Johnson syndrome has been associated with ramipril therapy.

Drug-induced pemphigus has also been associated with a related drug, captopril[6]. The mechanism remains unknown but drugs containing a thiol group may be involved as they are able to produce acantholysis of epidermal cells *in vitro*. Drugs containing an amide group have also been associated with pemphigus. These include enalapril which also induced acantholysis *in vitro*. Four cases of enalapril-induced pemphigus have been reported[7]. Spontaneous remission of the skin lesions after drug withdrawal is less common with drugs containing the amide group compared with drugs containing the thiol group. Some cases of flares of pustular psoriasis with ramipril and captopril use in psoriatic patients have been reported[8]. The mechanisms for ACE inhibitor-induced adverse reactions in the skin are mostly based on non-immunological mechanisms. Researchers have demonstrated the expression of a complete renin-angiotensin system in human skin,

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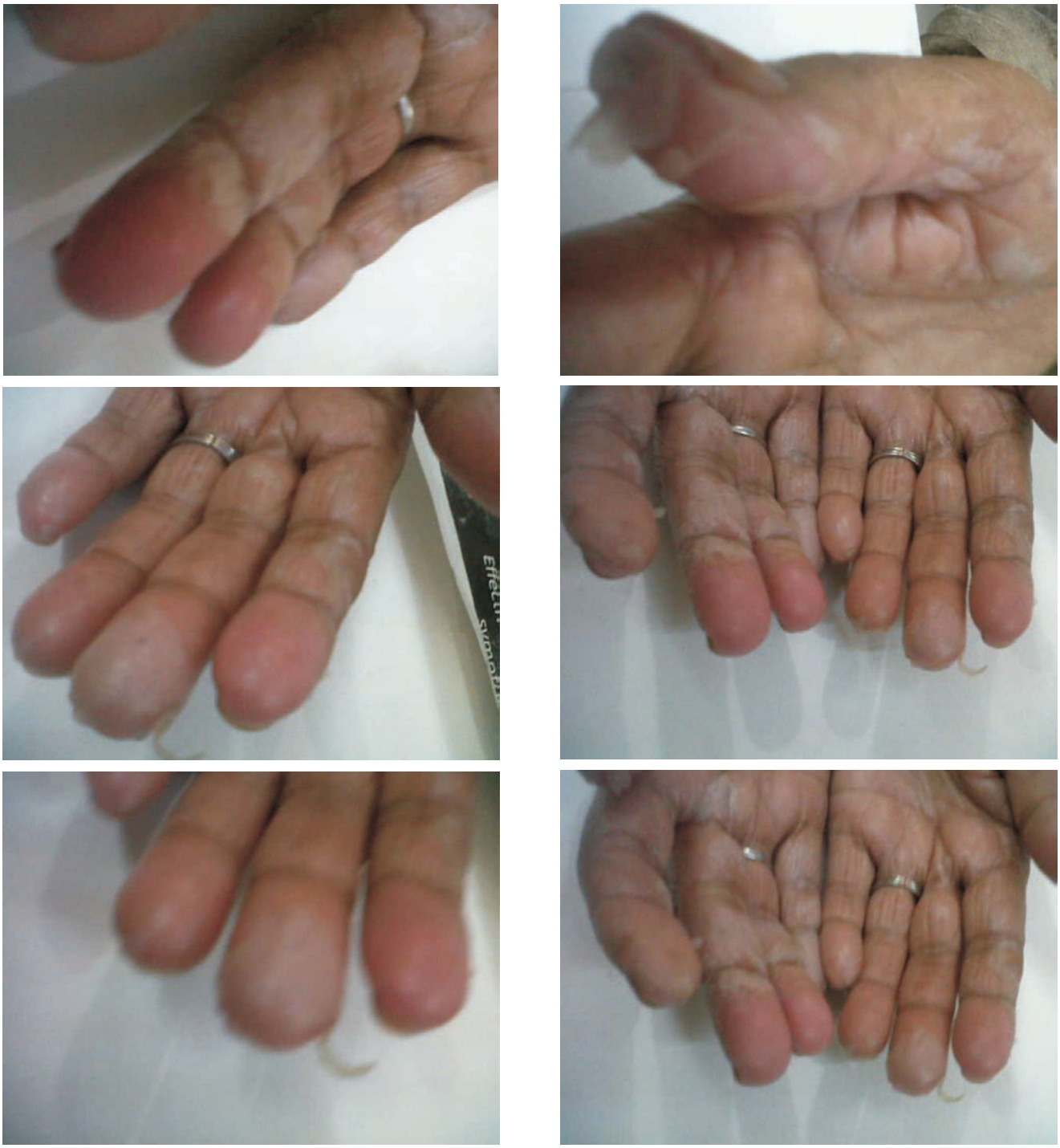

Fig. 1-6: *Skin eruptions caused by ramipril in our patient.*

including the precursor of angiotensin II, angiotensinogen, renin, angiotensin converting enzyme, and receptors of the AT1 and AT2 receptor subtype, but their function is unknown4. Other common side effects of ACE inhibitor therapy are dry cough (found in 20% of cases), hypotension, hyperkalaemia, renal failure, dysgeusia (gustatory hallucination), proteinuria, agranulocytosis. Other uncommon adverse effects are headache, dizziness, fatigue, nausea, diarrhoea, impotence, loss of libido, myalgia, muscle cramps, hair loss, hepatitis, cholestatic jaundice, acute pancreatitis, and the occurrence of anti-nuclear antibodies[9].

Conclusion

To conclude our case regarding this rare skin manifestation of ramipril, we wish to emphasise that these skin manifestations can be reversed within a short span of time if recognised early.

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"A wise man ought to realise that health is his most valuable possession."

– Hippocrates (c. 460-357 BC):
A Regimen for Health.

CASE REPORT

JIACM 2013; 14(2): 184-6

Concomitant occurrence of cryptococcal meningitis and tuberculous meningitis in a HIV-negative patient with alcoholic cirrhosis and Pott's spine

Nitya Nand, Parveen Malhotra**, Dipesh Dhoot***, Renu Bansal****

Abstract

Cryptococcus neoformans is an encapsulated yeast that causes serious infections in immunocompromised populations. The majority of cases occur in HIV-infected individuals. Mycobacterium tuberculosis is another very common opportunistic infectious agent in HIV population as well as in immunocompetent population. Many cases of mixed infections have also been reported in immunocompromised patients especially HIV-positive patients but all of them having infections at two different sites. Mixed CNS infections in a HIV-negative patient has never been reported before. We report here a case of a 41-year-old, HIV-negative man with alcoholic liver cirrhosis with chronic hepatitis C who presented with seizure and unconsciousness. Cryptococcal meningitis with tuberculous meningitis (cerebral tuberculosis) with Pott's spine was diagnosed, and despite adequate treatment the patient developed multi-system organ failure and eventually expired.

Key words: Tuberculous meningitis (cerebral tuberculosis), cryptococcal meningitis, cirrhosis-associated immune deficiency syndrome.

Introduction

Cryptococcus neoformans is an ubiquitous encapsulated yeast that predominately causes significant infections in immunocompromised individuals, with eighty to ninety per cent of all cases occurring in those with HIV infection. The most common forms of infection are meningitis and lung infections. *Mycobacterium tuberculosis* is also a common opportunistic infective agent in form of tuberculous meningitis, pulmonary tuberculosis, and spinal tuberculosis in HIV patients. Concomitant occurrence of these two types of CNS infections is very rare, even rarer is their occurrence in HIV-negative patients. Here, we report a case of cryptococcal meningitis with tuberculous meningitis, occurring in a HIV-negative patient with alcoholic liver cirrhosis.

Case summary

A 41-year-old chronic alcoholic and a diagnosed case of chronic hepatitis C with liver cirrhosis presented to the emergency department with a 5-month history of jaundice and backache with reduced sleep and altered behaviour since last 6 - 7 days followed by 15 - 16 episodes of seizures and loss of consciousness on the day of presentation. The patient was also having constipation since the last 4 - 5 days which suggested hepatic encephalopathy as the probable cause of his present complaints.

His past history was notable for few episodes of seizures in the last 2 years with a correlation with failed attempts to abstinence and similar history of abstinence followed by seizures was seen in the current episode of illness also. Hence a differential diagnosis of alcohol withdrawal seizures with post-ictal unconsciousness was also kept.

On physical examination, the vital signs showed a temperature of 37°C, heart rate of 100 beats/min, blood pressure of 130/78 mmHg, and respiratory rate of 16 per min. General examination revealed pallor but no icterus. Chest auscultation was normal and the cardiac rhythm was regular with a normal rate. No murmurs were appreciated. His abdomen was soft, non distended with no evidence of ascites. Guarding, rebound tenderness, and hepatomegaly were not appreciated but moderate splenomegaly was present. Neurologic examination revealed reactive pupils and movement of the extremities only in response to painful stimuli. The Glasgow coma scale score was 9/15. No asymmetry or focal neurological sign was appreciated.

Laboratory studies revealed a white blood cell count of 6,000 cells/cumm, with 78% polymorphonucleated cells, and a platelet count of 60,000 per cumm. His INR was 2.63. An extended metabolic and liver panel demonstrated: serum sodium 137 meq/l, blood urea 22 mg/dl, serum creatinine 1.2 mg/dl, serum total bilirubin 2.0 mg/dl, aspartate transaminase 34 U/l, alanine transaminase 15 U/l, and alkaline phosphatase 72 U/l. HIV antibody and hepatitis B surface antigen by ELISA was found to be negative, and anti-HCV was positive.

A MRI of the lumbo-sacral spine for backache was done 2

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months ago which showed collapse of D12, L2, L4, and L5 vertebal bodies (Fig.1) with associated prevertebral soft tissue thickening suggestive of spinal tuberculosis. He had not received any anti-tuberculous therapy (ATT) during this 2-month period. In view of his spinal TB and no response to conservative therapy, a lumbar puncture was done and cerebro-spinal fluid (CSF) examination showed raised proteins (155 mg %) with lymphocytic pleocytosis. Gram's stain showed budding yeast cells and Ziehl-Neelsen staining showed acid-fast bacilli in CSF. India ink preparation was examined to reveal the presence of *Cryptococcus neoformans*. Adenosine deaminase (ADA), polymerase chain reaction (PCR), or cryptococcal antigen tests were not done due to non affordability by the patient.

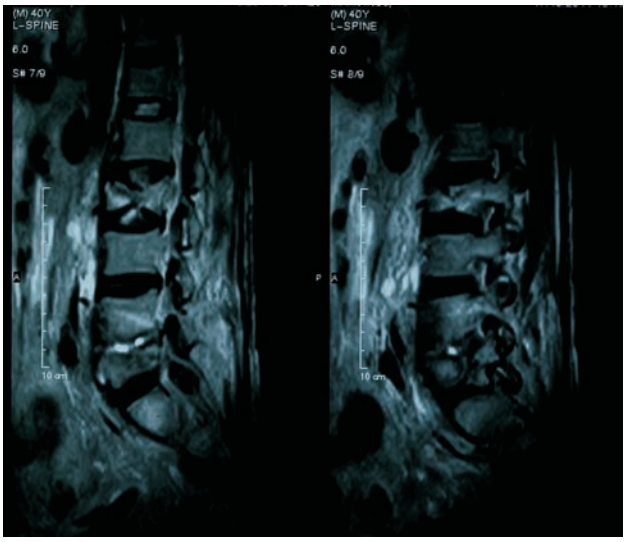

Fig. 1: *MRI of the lumbo-sacral spine showing collapse of D12, L2, L4, and L5 vertebral bodies.*

The patient was started on ATT and amphotericin B, and serial liver and kidney function tests were done at regular intervals. Six days after starting ATT, the patient's serum bilirubin started to increase and ATT was modified accordingly to ethambutol 800 mg OD, streptomycin 750 mg OD and ciprofloxacin 500 mg. 3 days later, renal functions also started deteriorating despite adequate hydration and urine output decreased, so streptomycin and amphotericin B were also withheld. Serum bilirubin came back to normal values in 5 - 6 days and low-dose isoniazid (INH) was again added to the medical regimen, but renal functions did not improve and the patient continued to deteriorate and eventually died.

Discussion

Cirrhosis-associated immune dysfunction syndrome (CAIDS) is a multifactorial state of systemic immune dysfunction, which decreases the ability to clear cytokines, bacteria, and endotoxins from the circulation. Thus cirrhosis is considered an immunocompromised state that leads to a variety of infections. Bacterial infections occur in 32% to 34% of admitted patients with cirrhosis[1] and in 45% of those with GI haemorrhage. These rates are drastically higher than the usual 5% to 7% overall rate of infection in hospitalised patients[2]. Pathogens such as *Mycobacterium tuberculosis, Clostridium difficile, Cryptococcus neoformans, Vibrio vulnificus, Yersinia enterocolitica, and Listeria monocytogenes,* are more common and virulent in patients with cirrhosis than in the general population. Mixed infections have been reported in very few patients – that too in HIV-positive patients only.

Cryptococcus neoformans is an encapsulated yeast that predominately affects immunocompromised individuals. In addition to HIV infection, immunosuppressive medications, solid-organ transplantation, chronic organ failure (renal and liver), haematologic malignancy, chronic lung disease, and rheumatologic disorders can also predispose individuals to this infection[3]. Although cryptococcal infection can affect any tissue or organ, the majority of cases involve the CNS and/or the lungs. The diagnostic gold standard for *Cryptococcus neoformans* infection is growth of the organism in culture.

Recommendations for the treatment of CNS disease are well established. Immunocompetent patients with cryptococcal meningitis should be treated with amphotericin B and flucytosine for 6 - 10 weeks, or amphotericin B and flucytosine for 2 weeks followed by fluconazole (400 mg/day) for a minimum of 10 weeks. For immunosuppressed patients without HIV infection, it is recommended that cryptococcal meningitis be treated with amphotericin B +/- flucytosine for 2 weeks followed by 8 - 10 weeks of fluconazole (400 - 800 mg/day), and then fluconazole (200 mg/day) for an additional 6 - 12 months.

The incidence and virulence of *Mycobacterium tuberculosis* infections are increased in patients with cirrhosis[4]. TB patients with liver cirrhosis show extra-pulmonary involvement more frequently[5]. The key to the diagnosis of TB is a high index of suspicion. Clinical findings include fever, headache, altered mental status, cough, nausea/vomiting, seizures, and meningismus. Diagnosis is dependent on CSF analysis. Culture is the gold standard, however it is insensitive and very slow (taking up to 6 - 8 weeks) to aid clinical decisions. The search for acid-fast bacilli (AFB) by direct Ziehl-Neelsen staining of the CSF represents the best rapid laboratory diagnostic technique[6]; however, this lacks sensitivity. In general examination of cerebrospinal fluid, a high leukocyte count (up to 1,000/μL) is usually seen with a predominance of lymphocytes. Polymerase chain reaction

(PCR) has a sensitivity of up to 80%, but rates of false-positivity reach 10%. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed. Hence a high clinical suspicion and early initiation of therapy is needed to recognise and treat patients effectively.

A few cases of mixed infections have been reported in immunocompromised patients – especially HIV-positive patients – but all of them were having infections at two different sites. Mixed CNS infections in a HIV-negative patient have never been reported before. Hence, the present case is the first-ever reported case of concomitant tuberculous meningitis with cryptococcal meningitis with spinal tuberculosis.

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"By medicine life may be prolonged,
yet death will seize the doctor too."

– William Shakespeare (1564-1616).

CASE REPORT

JIACM 2013; 14(2): 187-9

Dengue fever with myocarditis

Atul Bhasin, Rakshit Kumar**, Kanika Chandra***, Rajinder Kr Singal*****

Abstract

We present here a case of a twenty-year-old female with dengue haemorrhagic fever (DHF). Patient developed hypotension and pulmonary oedema that was aetiologically conferred to be myocarditis (based on raised cardiac enzymes and global hypokinesia on echocardiography). Patient improved clinically with resolution of cardiac dysfunction with supportive management. The case emphasises the suspicion of myocardial damage as the confounding pathology in dengue infection mimicking dengue shock syndrome (DSS).

Key Words: Dengue fever, shock, myocarditis.

Introduction

Dengue, an arboviral disease caused by a flavivirus is transmitted by the *Aëdes aegypti* mosquito. Dengue virus has four antigenically distinct serotypes (DEN 1, DEN 2, DEN 3, and DEN 4). Dengue may remain asymptomatic or manifest as undifferentiated fever (or viral syndromes), dengue fever, dengue shock syndrome (DSS), or dengue haemorrhagic fever (DHF). An increasing number of cases of dengue are being reported with atypical presentations as frequent epidemics are occurring. As awareness of this disease is increasing, rare manifestations are also being reported.

Case report

A twenty-year-old female admitted in a nursing home three days back with complaints of fever and myalgia of two days, developed hypotension despite adequate fluid management and her investigations revealed progressive thrombocytopenia with positive dengue serology IgG. She developed acute breathlessness over the past 24 hours along with one episode of coffee coloured vomiting and passing black stools and then she was transferred to our hospital for further management. On arrival at the triage in our hospital, examination revealed a toxic and dyspnoeic patient with a pulse rate of 134/min, BP of 86/66 mm of Hg and cold extremities, there was no pallor, cyanosis, icterus, clubbing, lymphadenopathy, or pedal oedema. Systemic examination revealed diffuse bilateral crackles up to mid-scapular region in the chest, and S3 gallop rhythm on cardiovascular system examination. Her abdomen was soft, with slight tenderness in the epigastric region. She was admitted in MICU and started on dobutamine infusion, subsequently noradrenaline infusion was added as she remained hypotensive. One unit of PRBC, SDP along with two units of FFP was started pending reports. IV pantoprazole, haemostatics, antiemetic, and O_2 therapy with nasal prong as supportive medication were started. Her haematological and biochemical investigations revealed severe thrombocytopenia (15,000) and raised transaminases. Her routine biochemistry was within normal limits but her CPK (421 U/l) and CPK MB (67.7 U/l) were raised and these increased mildly after 12 hrs to CPK - 429 U/l, CPK MB - 69.4 U/l. Her chest skiagram (Fig. 1A) showed evidence of pulmonary oedema with no cardiomegaly, suggestive of acute left ventricular failure. An urgent echocardiography was advised which revealed normal-sized chambers with mild MR and trace TR (RVSP 30 mm of Hg), global hypokinesia and EF of 40 - 45%. USG abdomen (Fig. 2) revealed moderate bilateral pleural effusion with moderate ascites and diffuse GB wall oedema. IVC size and respiratory collapse of IVC (Fig. 3) were normal on USG abdomen suggesting no evidence of RV failure. Her D-dimer was positive (2.34). Malaria antigen and Typhi dot were negative. There was no evidence of any bleed after the first episode. Dyspnoea, tachycardia, hypotension got

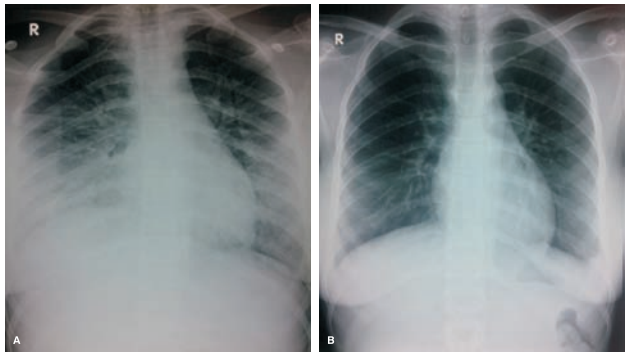

Fig. 1: *Chest skiagram of patient* ***(A)*** *On admission showing pulmonary oedema with normal cardiac size;* ***(B)*** *Normal lung parenchyma on discharge.*

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stabilised and vasopressor support was tapered-off after 72 hours. She was shifted to the ward on stabilisation, with a platelet count of 1,38,000/cumm. On discharge, her chest skiagram (Fig. 1B) became normal and echocardiography (Fig. 4) revealed normal EF of 55% , with no evidence of regional wall motion abnormality or regurgitant flow on colour Doppler. In view of the above clinical scenario with positive dengue serology, raised cardiac markers and echocardiography findings which improved on convalescence, a diagnosis of dengue myocarditis was made. The patient comes for routine follow-up and is presently asymptomatic.

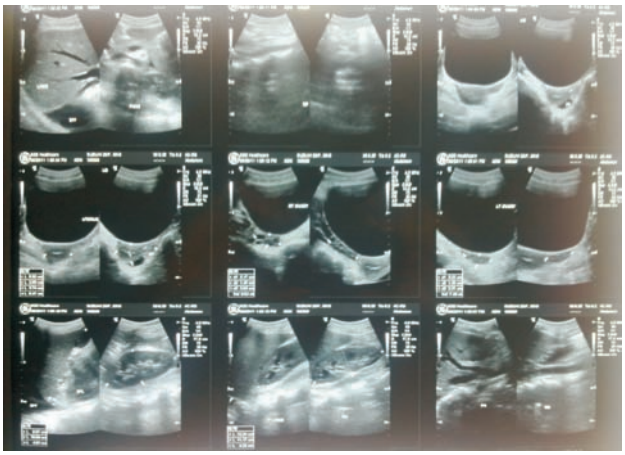

Fig. 2: *USG showing ascites and pericholecystic oedema suggestive of features of dengue fever.*

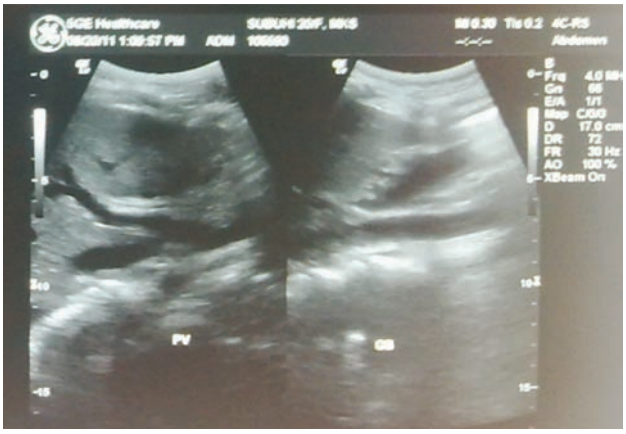

Fig. 3: *USG showing normal IVC size suggestive of normal RV pressure.*

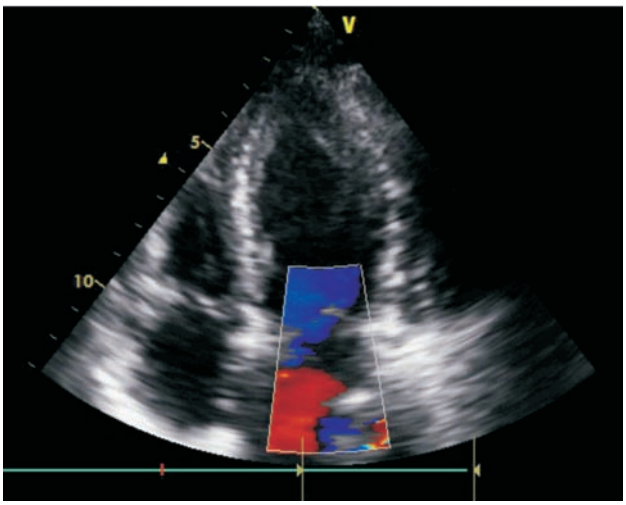

Fig. 4: *Echocardiography of the patient.*

Discussion

Myocarditis or inflammation of the myocardium associated with infectious diseases especially dengue and Chikungunya fever is well recognised but is a very rare manifestation of the disease. Thought to be a benign disease, it has been now reported as a chronic disorder, and rarely leading to cardiomyopathy. Rhythm disturbances manifesting as sinus tachycardia, sinus bradycardia, atrioventricular conduction disturbances, atrial fibrillation along with atrial and ventricular ectopic beats are the most common presentation during the acute and convalescence phase. Acute myocarditis presenting as acute myocardial infarction has also been reported. In most of the reported cases, there were no documented electrolyte disturbance[1]. Myocardial damage is a very rare entity, as is a direct consequence of virus invasion causing damage to the muscle fibres. Hypersensitivity or autoimmune reaction damage has also been postulated; as the insult may persist, it makes the myocardium prone to recurrent damage. Pericardial involvement has also been attributed to dengue infection along with myocarditis. The symptomatology is so vague and non-specific that unawareness of its existence in relation to a particular infection may lead to a missed diagnosis. Pathological mechanism and the incidence of myocardial manifestations is obscure. Though in many cases the disease is self limiting, occasionally it may causes fatal myocarditis. The pathogenic mechanism of cardiac dysfunction is not well established though altered autonomic tone and prolonged hypotension may play a significant role. Post mortem autopsies conducted revealed distinct histological changes in the myocardium showing interstitial oedema with inflammatory cell infiltration and necrosis of myocardial fibres. Significant histo-pathological changes were also seen in the lungs, liver, brain, and spleen[2]. Direct demonstration of dengue viral infection of myocardium shown with immuno-histochemistry, was used to demonstrate direct dengue viral infection in the myocardial tissues causing myocarditis. Derangement of calcium storage in the infected cells also contributes to the myocardial damage[3]. Another study demonstrated presence of dengue viral antigen in the liver, spleen, lungs, kidneys, and peripheral

blood leucocytes, but not in thymus, lymph nodes, thyroid, pancreas, heart, adrenal gland, skeletal muscles, intestine, and brain[4]. This property of the dengue virus needs to be further evaluated. Myocardial dysfunction is seen in patients with DHF and in approximately 20% of these, LV ejection fractions are less than 50%, which return to normal within a few weeks. Arbovirus myocarditis as a sequel in patients suffering with dengue has now been a known complication in a chronic form[5]. Patients with severe dengue have evidence of systolic and diastolic cardiac impairment, with the septal and right ventricular wall being predominantly affected[6].

Table I: Investigations.

	19/9	20/9	21/9	22/9	23/9	24/9	26/9
Hb g/dl	12.7	11.8	13	12.6			
PCV	36.7	33.9	39.2	37.0			
Platelet count/cumm	15,000	31,000	30,000	52,000	73,000	1,38,000	2,57,000
TLC	7,300	10,000		5,300			
CPK (MB) U/l	67.7	69.4		34.4			20.3
CK U/l	421	429		211			87

To conclude, dengue fever can have varied and multi-systemic presentation with typical and atypical manifestations. Atypical presentation of myocardtis can mimic DSS or respiratory distress, primarily due to increased fluid permeability and leak from alveolar-capillary membrane. Early recognition of myocarditis as atypical presentation is imperative in the management of dengue shock syndrome. Thus an entity of primary cardiac failure due to myocarditis in dengue infection needs to be evaluated early for proper management and outcome.

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"He who has health has hope,
and he who has hope has everything."

– Arabian Proverb.

CASE REPORT

JIACM 2013; 14(2): 190-1

Klebsiella infection-associated autoimmune haemolytic anaemia

Afsana Jahan, Euden Bhutia**, Tribhuvan Pal Yadav****

Abstract

Autoimmune haemolytic anaemia may be idiopathic or secondary to various causes and cold and warm antibody mediated. We report a case of cold agglutinin positive autoimmune haemolytic anaemia which was diagnosed to be due to Klebsiella infection after ruling-out other causes that have been reported earlier. The patient continued to have haemolysis even after treatment of the underlying infection, intravenous methylprednisolone pulse and intravenous immunoglobulin. He responded to plasmapheresis with resolution of haemolysis and there was no further need of haemolysis.

Key words: Autoimmune haemolytic anaemia, cold agglutinin, Klebsiella, plasmapheresis.

Introduction

Autoimmune haemolytic anaemia is a group of disorders that may be described on the basis of type of antibody responsible as cold and warm antibody mediated or according to underlying aetiology as primary or secondary. It is diagnosed by presence of severe anaemia, normocytic normochromic anaemia, reticulocytosis, indirect hyperbilirubinemia, raised lactate dehydrogenase (LDH) level and positive direct (DCT) and indirect Coombs' test (ICT).

Cold agglutinin associated autoimmune haemolytic anaemia is a condition where cold reactive antibodies acting at 4 degree centigrade account for the haemolysis. These antibodies are of IgM type and are large enough (size: 1,000 kD) to bridge the intercellular space between the red cells. This condition has most commonly been reported following viral infections, mycoplasma pneumonia, and infectious mononucleosis[1]. They may also occur in normal adults mostly in the seventh decade of life[2], in association with lymphoproliferative disorders[3] and various other infections like hepatitis A, C[4] and human immune deficiency virus[5]. To the best of our knowledge, this has never been reported in association with Klebsiella infection; here we report a case.

Case report

A 13-year-old male child was admitted with continuous high-grade fever, without chills and rigors of 5 days duration along with progressive weakness, difficulty in breathing, and yellowish discoloration of urine and eyes for 2 days. There was no history of loose stools, dysuria, cough, sore throat, boils, and pain abdomen. There was no past history of blood transfusion, jaundice, rash, bleeding from any site, or passing black-coloured stools, and no family history of haematological abnormality or jaundice. At admission he had severe pallor, icterus, tachycardia (heart rate: 112/min), tachypnoea (respiratory rate: 34/min), blood pressure: 120/40 mmHg, hepato-splenomegaly (liver – 3 cm below costal margin, soft, tender; spleen – 2 cm below costal margin, soft, non tender) without significant lymphadenopathy. Cardio-vascular, respiratory, and central nervous system examinations were normal. Investigations showed haemoglobin: 4.9gm/dl; total leukocyte count: 14,200/cumm; differential leukocyte count: polymorphs-48, lymphocytes-50, eosinophils 2; platelet count: 4,00,000/cumm; reticulocyte count: 25%; peripheral smear: features of haemolysis and no haemoparasite seen; serum bilirubin: 4.8 (indirect: 4.2) mg/dl; LDH: 2,565 IU/l, negative malaria card test, normal urine (routine and microscopy; prothrombin time (PT): 19.4 sec; activated partial thromboplastin time (APTT): 34 sec; INR: 1.35; DCT and ICT were strongly positive; glucose-6-phosphate dehydrogenase (G-6PD) level was normal, hepatitis B surface antigen (HbsAg), IgM against hepatitis A, E, C, and widal test were negative. Patient was started on injection ceftriaxone and amikacin in view of the possibility of severe sepsis. Blood transfusion was given for the severe anaemia. His HIV by ELISA, Monospot test, IgM antibody against *Legionella pneumophilia, Mycoplasma pneumoniae, Leptospira, Chlamydia pneumoniae*, adenovirus, respiratory synctial virus (RSV), influenza and parainfluenza virus, anti-nuclear antibody and Ham test (acidified serum test) were negative. His blood culture grew Klebsiella sensitive to ciprofloxacin, amikacin, piperacillin, linezolid, and clindamycin. Based on this, his antibiotics were switched to ciprofloxacin and clindamycin. Bone marrow examination revealed normal normoblastic reaction.

Though the fever responded, anaemia did not improve

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and haemoglobin was still low (4.3 gm/dl) despite four units of packed cell transfusion. We could not give further blood transfusion as cross-matching was not possible due to high level of antiglobulin antibodies. Further evaluation revealed a positive cold agglutinin test. Hence a diagnosis of cold agglutinin positive immune haemolytic anaemia probably due to Klebsiella infection was made. He was kept in warm environment and all intravenous drugs and fluids were pre-warmed. He was given intravenous methylprednisolone pulse therapy (30 mg/kg/day) followed by oral prednisolone. He also received intravenous immunoglobulin over the next two days (2 gm/kg) but his haemoglobin continued to drop (2.9 gm/dl) and he developed congestive cardiac failure, and haemolysis continued. Hence it was decided to subject the patient to plasmapheresis. He required four more sittings of plasmapheresis. After this the patient's haemoglobin started rising and no further packed cell transfusion was needed. However, DCT/ICT continued to be positive. The patient received antibiotics for a total period of 2 weeks and prednisolone (1 mg/kg/day) for 2 weeks after which it was tapered over the next 2 weeks and stopped. At discharge after 3 weeks of hospital stay, his haemoglobin was 11.1 gm/dl with no evidence of haemolysis and failure; his DCT was positive but ICT became negative

Discussion

Cold agglutinin autoimmune haemolytic anaemia is IgM-mediated and these antibodies are of monoclonal type, reactive at low temperature. Direct and indirect Coombs' tests are positive. Corticosteroids and intravenous immunoglobin are the mainstay of treatment though they are less effective in cold antibody mediated haemolysis, and the disease course is usually prolonged[6]. Anti CD 20 molecule rituximab has been used in cold and warm agglutinin disease[7]; the main disadvantage with their use is possibility of flare-up of any underlying infection. Plasmapharesis has been used as a treatment modality especially in cortisteroid unresponsive cases in lymphoproliferative disease associated cold agglutinin haemolysis[8].

Our patient, who developed immune haemolysis possibly following Klebsiella infection, had severe ongoing haemolysis, so that even after four units of packed cell transfusion, haemoglobin did not increase, DCT/ICT continued to be highly positive and cross-matching with same blood group was not possible. Immune haemolysis due to Klebsiella infection has never been reported. Despite receiving adequate intravenous antibiotics followed by methylprednisolone pulse therapy and intravenous immunoglobulin, he continued to have severe anaemia with congestive cardiac failure; therefore plasmapharesis was performed. Rituximab or immunosuppressives were not preferred since the patient had underlying sepsis. The patient responded to this modality of treatment with rise in haemoglobin, normalisation of reticulocyte count, and resolution of features of haemolysis in the peripheral smear.

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"No friend like health abounding;
and like disease no foe."

– Panchatantra.

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Non-healing foot ulcers in rheumatoid vasculitis

Arun Gogna, Susheel Kumar Sharma**, Abhishek Shridhar****

A 62-year-old woman with long-standing seropositive (ACPA and RF positive) rheumatoid arthritis and hypertension presented with 2-weeks of breathlessness and 3-years of non-healing foot and leg ulcers which failed to respond to repeated courses of antibiotics (Fig. 1).There was no peripheral neuropathy or leg ischaemia on arterial Doppler scan. Her synovitis was quiescent and she was on prednisolone 10 mg/day , methotrexate 7.5 mg/week and amlodipine plus atenolol with good blood pressure control. Her Hb was 7 gm%, TLC - 26,000/cumm and platelets 21,000/cumm. KFT and serum proteins were normal, and blood culture for pyogenic organisms was sterile. CRP was markedly raised (98.40 mg/l) while X-ray chest PA view and serum procalcitonin levels (0.15 µg/l) were normal. Echo showed mild LVH, global LV hypokinesia with LVEF 45% and minimal pericardial effusion. Her total serum IgG was 20.18gm/l.

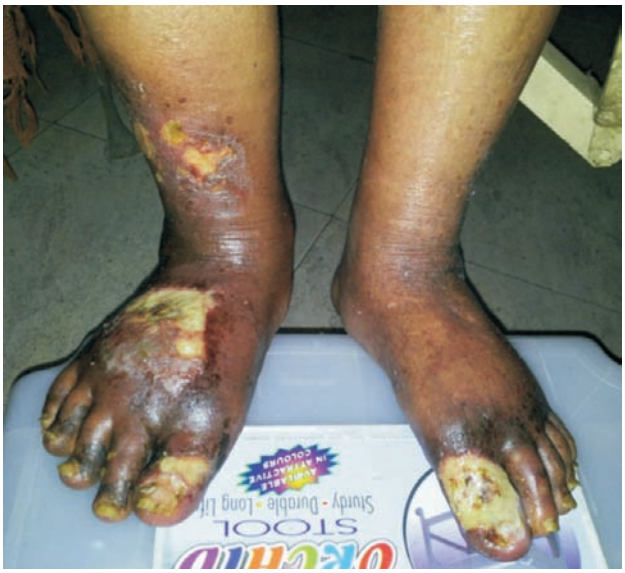

Fig. 1: *Leg and foot ulcers before rituximab therapy.*

She was diagnosed to have rheumatoid vasculitis as a cause of her non-healing leg and foot ulcers and was given 500 mg of rituximab with a repeat dose after 2 weeks. There was remarkable improvement in the leg and foot ulcers which showed healing phase with granulation towards the end of second week following the first infusion of rituximab (Fig. 2) and her breathlessness settled. Her haemoglobin improved to 10.5 gm%, TLC

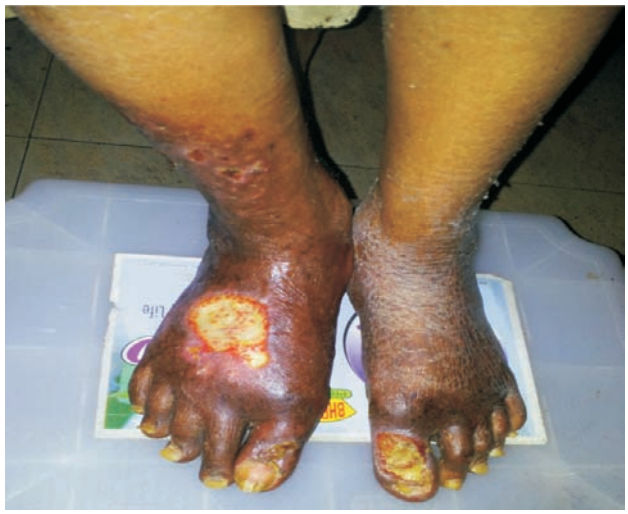

Fig. 2: *Leg and foot ulcers two weeks after rituximab therapy*

decreased to 9,600/cumm and platelets rose to 2,34,000/cumm. CRP dropped to 29.4 mg/l. A repeat echo study showed rise of the LVEF to 60% and resolution of the pericardial effusion.

Rheumatoid vasculitis can occur with quiescent synovitis and cause non-healing leg and foot ulcers[1]. It can be treated with high doses of systemic steroids, cyclophosphamide, or rituximab. In elderly patients, high dose of corticosteroids and cyclophosphamide have considerable toxicities. Rituximab is costly, but a one-time administration which can be done on day care basis also, reduces hospital stay and a cost-cutting dose of 500 mg x 2 has been found to be as effective as 1,000 mg x 2 doses[2] and response after the first dose can be remarkable in responders[3].

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