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Journal, Indian Academy of Clinical Medicine • Vol. 12, Number 2, April – June, 2011

Contains 76 pages from 89 to 164 inclusive of all advertisements

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VIEWPOINT

JIACM 2011; 12(2): 100-01

What we Need is Not the Will to Believe but the Will to Find Out

*BM Hegde**

"The illogical man is what advertising is after. This is why advertising is so anti-rational; this is why it aims at uprooting not only the rationality of man but his common sense."

– Henryk Skolimowski.

There are demands growing all over the world for rationality in medical interventions these days, not the least in the UK and the USA. In fact, the first editorial in the *British Medical Journal* for the year 2011, published during the first week of January, is on rationality in medical interventions. I congratulated the editor for her bold stand on opening the Pandora's box on *rationality in medical interventions* – drugs or surgery. Going through the history of the word rational, I found that way back in 1803, the meaning was: "to explain, to make reasonable;" in the psychological sense of "*to give an explanation that conceals true motives.*" It dates from 1922.

There is a nice movie – Big Bucks, Big Pharma – on this topic which is worth watching. I shall give the readers a glimpse into that movie here. "Big Bucks, Big Pharma", pulls back the curtain on the multi-billion dollar pharmaceutical industry to expose the insidious ways that illness is used, manipulated, and in some instances created, for capital gain. Focusing on the industry's marketing practices, media scholars and health professionals help viewers understand the ways in which direct-to-consumer (DTC) pharmaceutical advertising glamorises and normalises the use of prescription medication, and works in tandem with promotion to doctors. Combined, these industry practices shape how both patients and doctors understand and relate to disease and treatment. *Ultimately, "Big Bucks, Big Pharma" challenges us to ask important questions about the consequences of relying on a for-profit industry for our health and well-being." (Italics mine!)*

There is an apt comment on this movie by an American movie critic: "In my opinion this is the best made film on our site today regarding the pervasiveness of drug companies in our everyday lives. The film starts with a narration by the famed journalist Amy Goodman but lets the interviews themselves narrate the film later on. Though this film doesn't address the subject directly, if you want to know why the United States of America doesn't provide universal healthcare, I think that you should watch this movie. Why should we have free or inexpensive healthcare if the current system is so profitable?!

I think our present therapeutics and its attendant pseudo-science would be correctly described by this meaning of the word 'rational'. The industry that tries the marketing strategy of rationalising drug pushing and disease mongering by concealing their true motive – to make the highest profit for themselves – can never be altruistic to listen to your sane advice. Your story of insulin pens was one such effort. Now many other drugs have come with pens! I am reminded of what Bernard Mandeville, the guru of Laissez Faire, when he wrote: "In the corporate economy profit is the sole motive irrespective of consequences." How very true? Mandeville was Adam Smith's teacher! Our drug cartels have taken his advice to their heart.

Taking your advice in the New Year I hope some one will come up with audits like the one which showed aspirin in its true colour for all the newly introduced drugs. Remember we have had digoxin for nearly 350 years from William Withering's time. Even now the DIG (digoxin investigation group) group recently failed to find out why digoxin is prescribed for heart failure patients in sinus rhythm? Why is the ADR (adverse drug reaction) death rate going up exponentially even with "so called" scientific

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advances in modern medicine? Was not Hillary Butler right in saying that the present modern medicine, which has become a corporate monstrosity, would have cut many James Wakelys in the knees. James Wakely was a young doctor in London and a member of the House of Commons who thought in the early nineteenth century that the medical profession at that time had become a bad abscess on the body of society which he wanted to cure by taking out the pus using a surgical lancet. He started the now famous medical journal *The Lancet* for that purpose in 1823 AD. He had assessed the profession at that time and thought that it also included some "incompetent, corrupt, and nepotistic bunch of crooks." Poor man, even after nearly two hundred years, the abscess that modern medicine then was, is only growing bigger by the day despite his *The Lancet*!

Even the President of NICE, Sir Michael Rawlins, in his Harveian oration at the Royal College, had this to say about RCTs: "*that randomised controlled trials (RCTs), long regarded as the 'gold standard' of evidence, have been put on an undeserved pedestal*". Sir Michael outlines their limitations in several key areas, arguing that a diversity of approaches should be used to analyse the whole of the evidence base. (Rawlins M. The Harveian Oration of 2008, De Testimonio. On the evidence for decisions about the use of therapeutic interventions. Royal College of Physicians, 2008).

Let me remind the readers that the "first pass effect" that we, medical students all over, memorised for the pharmacology examination must have given us the warning that all (I mean all) reductionist chemical molecules, ranging from aspirin to rosiglitazone, are alien to the human system. The body tries to get rid of them. This has now been demonstrated by Douglas C Wallace using his software MITCHIP to be true! (*Genetics* 2008; 179: 727) You will have the same story for your editorial every year-end to welcome the next 'New Year', if we do not learn from our mistakes. We need another George Bernard Shaw to write a drama on 'Patients' Dilemma' today.

When you watch the movie cited above, you will come to know how lay people are brainwashed to ask for those wonder drugs, advertised daily as panacea for this or that disease, from their doctor. Many a times it is likely that one might even imagine a disease (disease mongering by the industry) to have the treatment "very early". How does the common man, even the literate one, survive in this polluted atmosphere where the industry and the profession seem to be in cahoots with one another for personal gain? To add to this, a new industry has grown around this rationality – corporate hospital industry – especially in the developing countries like India, where even today more than 400 million people get less than one clean nutritious meal a day. 67 million children suffer from nutritional immune deficiency syndrome (NIDS) dying by the thousands daily! Let us have a heart.

"Appeals to rationality are mostly bluff. There is no good theory of what it is nor of how to recognise it."

– DH Mellor.

ORIGINAL ARTICLE

JIACM 2011; 12(2): 102-05

QT-dispersion in Patients with Stroke without Known Cardiac Disease

SN Chugh, Arvind Garg**, Amit Yadav**, Surabhi Yadav****

Abstract

***Background:** QT-dispersion represents interlead variability of QT interval and reflects heterogeneity of myocardial repolarisation. Abnormalities in electrocardiogram (ECG) are common in acute cerebrovascular events (CVA) like ST and T wave changes. However, changes in QT-dispersion are also reported recently.*

***Objective:** To investigate if QT-dispersion is increased in patients who had an acute stroke and if this is associated to the extent or localisation of stroke.*

***Material and methods:** We included 100 patients of acute stroke with no previous history or sign and symptoms of cardiovascular disease. 50 age and sex matched controls were also taken.12 lead ECGs were recorded within the first 24 hours (24 hour ECG) and between 72 and 120 hours (72 hour ECG) from stroke onset. QTcd (corrected QT interval) was assessed by single observer blinded to the clinical data.*

***Results:** In our study, QTcd was increased significantly in the 24 hour ECG in patients compared to controls and QTcd decreased and became comparable to controls at 72 hours. QTcd was also significantly higher in patients having a right-sided lesion compared to a left-sided lesion, in patients with haemorrhagic lesion compared to infarct and in patients with a large lesion compared to a small lesion.*

***Conclusion:** QTcd is increased at 24 hours in patients with acute stroke and the increase was more in patients with a right-sided lesion, a haemorrhagic lesion and in patients with a large lesion. QTcd decreased and became comparable to controls at 72 hours.*

Introduction

Increased QT-dispersion (QTd) on the surface electrocardiogram is considered a measure of repolarisation inhomogeneity of the myocardium that could represent an electrophysiologic substrate for ventricular arrhythmia[1]. It has been defined in a variety of cardiac and non-cardiac diseases and is reported to be a non-invasive risk marker for arrhythmia and mortality in many diseases[2].

There is evidence for an interaction between the central nervous system (CNS) and cardiovascular system during acute cerebrovascular accidents/events (CVAs)[3]. Although ST segment and T wave changes in the ECG are well known consequences of stroke, arrhythmia and cardiac autonomic changes have also been reported[4]. The pathology of the above changes is still unclear and may be related to cardiac dysautonomia[5]. Cardiovascular functions are modulated by the CNS through the activity of brainstem and hypothalamus, and abnormalities in this pathway may be causative of these changes[6]. This study was designed to assess the QT-dispersion in patients with acute stroke without known prior cardiac disease.

Material and methods

The study included 100 patients of acute CVA with age more than 18 years admitted to Department of Medicine, Pandit BD Sharma PGIMS, Rohtak. Fifty healthy volunteers served as controls.

Patients who presented within 24 hours of onset of signs and symptoms of stroke and had no history of any ischaemic or cardiac disease were included.

Exclusion criteria

Patients who presented later than 24 hours of symptom onset were excluded. Similarly, the patients who died before 72 hour of symptom onset, who has lacunar stroke or had transient ischaemic attack (TIA) were excluded. All patients having a history of ischaemic, valvular, or hypertensive heart disease, heart failure due to any cause, severe respiratory failure, diabetes mellitus, renal or hepatic dysfunction were excluded. Patients taking any drug known to affect cardiac repolarisation like digoxin, antiarrhythmics, phenothiazine, tricyclic antidepressants, lithium carbonate, erythromycin, theophylline, and levodopa were excluded.

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Control group

Fifty healthy volunteers matched for age and sex contributed the control group to provide the normal QT-dispersion for comparison.

A complete neurological examination was performed at the time of enrolment in the study and after 72 hours. Patients underwent cranial computed tomography on enrolment. Repeat CT or MRI was done whenever deemed necessary. Patients were then divided into total anterior circulation infarct, partial anterior circulation infarct and posterior circulation infarct according to criteria proposed by Benford[7] *et al*. Patients who had haemorrhage on CT were divided into those having large (> 33 mm with or without ventricular extension) and small (haemorrhage size < 33 mm) haemorrhage[8].

12-lead surface electrocardiograms were recorded with the ECG machine keeping a fixed paper speed of 25 mm/sec and standardisation of 1 mm as 1 millivolt. ECG was recorded within 24 hours and again between 72 and 120 hours of symptom onset. ECGs for all patients and controls were recorded using the same ECG machine. All ECGs were assessed by a single investigator. All the measurements were done using a magnified scale by a single observer. The QT interval was measured from the onset of QRS complex to the point of T wave offset, defined as the return of T wave to baseline. In the presence of U wave, the nadir between T and U wave was taken.

QT intervals thus obtained were corrected for heart rate using Bazett's formula[9], i.e., QT duration divided by square root of RR interval ($QTc = QT/\sqrt{R - R}$) both in seconds. Only ECG with 9 or more leads having measurable QT interval were taken. QT-dispersion was calculated as the difference between the maximum (QTc_{max}) and minimum (QTc_{min}) value of QTc interval calculated in selected leads except lead avR.

Statistical analysis

The data between patients subgroups were tested by using student's unpaired 't' test and significance of difference between two consecutive ECG parameters in the same patients was tested by using student's paired 't' test.

Results

The present study included 100 patients of acute stroke above 18 years of age. Patients likely to have any other cause of altered QT-dispersion were excluded as per exclusion criteria.

All patients were subjected to a CT scan to document stroke and know the type of lesion. Simultaneous 12-lead surface ECG was taken within 24 hours of symptom onset (labelled as 24 hour ECG), and second ECG was taken between 72 and 120 hours of symptom onset (labelled as 72 hour ECG).

All controls were also subjected to 12-lead ECG. The patients were subdivided into various groups, i.e., whether having haemorrhagic lesion (N = 24) or ischaemic lesion (N = 76), whether lesion was right-sided (N = 55) or left-sided (N = 45), whether lesion was small (N = 54) or large (N = 46).

QT interval was measured from a minimum of 9 selected leads showing good T wave offset, and QTc was calculated using Bazett's formula ($QTc = QT/\sqrt{R - R}$)[9].

The maximum and minimum value of corrected QTc (QTc) was calculated in each ECG and QTc-dispersion (QTcd) was determined as the difference between maximum QTc (QTc_{max}) and minimum (QTc_{min}). The results thus obtained are shown in Table I.

The QTcd at 24-hour ECG was significantly higher than control and 72-hour ECG, but there was no significant difference between QTcd at 72-hour ECG in patients and controls.

The mean value of QTcd was significantly higher in patients with a large lesion compared to patients with a small lesion. Patients with haemorrhagic lesion had higher QTcd than patients with ischaemic lesion. Similarly patients with a right-sided lesion had higher QTcd than patients with a left-sided lesion.

Discussion

QT interval on ECG represents total duration of ventricular depolarisation and repolarisation. QT-dispersion represents increased variation or heterogeneity of ventricular repolarisation and is a risk factor for ventricular

arrhythmias. The QT interval has been found to be increased in various diseases like coronary artery disease, left ventricular hypertrophy, congestive heart failure, diabetes mellitus, renal failure, etc[6,10].

Table I: QT-dispersion (QTcd) according to stroke type and lesion localisation in 24-hr ECG and 72-hr ECG.

	24-hour	**ECG**	
	Large lesion (n = 46)	**Small lesion (n = 54)**	**P value**
QTcd (ms)	70.60 ± 18.21	48.66 ± 10.18	< 0.01
	Right-sided lesion (n = 55)	Left-sided lesion (n = 45)	
QTcd (ms)	62.85 ± 16.55	53.75 ± 18.79	< 0.05
	Haemorrhagic lesion (n = 24)	Ischaemic lesion (n = 76)	
QTcd (ms)	68.83 ± 19.00	55.58 ± 16.88	< 0.001
	72-hour	**ECG**	
	Large lesion (n = 46)	**Small lesion (n = 54)**	**P value**
QTcd (ms)	35.48 ± 14.06	38.85 ± 7.86	NS
	Right-sided lesion (n = 55)	Left-sided lesion (n = 45)	
QTcd (ms)	40.16 ± 10.42	26.60 ± 6.61	< 0.01
	Haemorrhagic lesion (n = 24)	Ischaemic lesion (n = 76)	
QTcd (ms)	38.42 ± 14.02	32.69 ± 9.81	< 0.05

As the heart has important and pronounced autonomic innervations, it is to be expected that neurovascular disturbances might result in a wide spectrum of cardiac function disorders. Patients with stroke have been found to have increased incidence of arrhythmia[11]. ST segment and T wave changes were known to be associated with acute stroke since long. In the present study we found that QTcd was significantly higher in patients at 24-hour ECG than controls and QTcd value becomes comparable to controls at 72 hours. Lazar *et al* also reported similar results[12]. In our study we also noticed that patients with a haemorrhagic lesion have a higher QTcd than patients with ischaemic lesion. The difference could be attributed to change in the geometry of the brain due to mass effect in case of haemorrhagic lesion. Patients with haemorrhagic stroke are also more prone to develop arrhythmia and may be related to prolonged QTcd[13]. Randell *et al* reported that patients with subarachnoid haemorrhage have increased QTcd compared with controls. They also observed episode of cardiac arrhythmia in these patients[14]. QTcd remained prolonged in patients with haemorrhagic lesion even at 72 hours compared to patients with ischaemic lesion whose QTcd became comparable to control. In our study we also noticed direct effect of size of lesion on QTcd, and QTcd was significantly higher in patients with a large lesion. Lateralisation of lesion has differential influence on the cardiovascular autonomic function[15]. A right-sided lesion particularly involving the insula has been shown to alter cardiac autonomic function more commonly than a left-sided lesion. Eckardt *et al* reported increased QTcd in patients who had a stroke that involved the insula. The mechanism by which QTcd is altered in patients with acute stroke is not well known, however, patients with stroke are known to have increased sympathetic activity, particularly nor-epinephrine, however catecholamine level did not correlate with QTcd interval probably due to inadequate study designe[15]. We also find QTcd to be higher in patients with right-sided lesion than in patients with left-sided lesion at 24-hours ECG, and the difference persisted at 72-hour ECG.

Conclusion

This study shows that QTc-dispersion increases in patients with acute stroke and the increase was more prominent in patients in the early period of stroke, patients with haemorrhagic lesion, patients with right-sided lesion, and patients with a large size lesion. These patients should be managed intensively, especially during the early period of the stroke.

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ORIGINAL ARTICLE

JIACM 2011; 12(2): 106-12

Comparison of Alprazolam and Low-dose of Risperidone as an Adjunctive Therapy to Enalapril in the Treatment of Mild-to-Moderate Essential Hypertension

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Abstract

Objectives: To compare the efficacy of alprazolam and risperidone with placebo as a part of adjunctive therapy to enalapril (as principal drug) in the management of mild-to-moderate essential hypertension.

Methods: Patients attending the cardiology OPD of the Himalayan Institute of Medical Sciences (HIMS) diagnosed as mild-to-moderate essential hypertension were enrolled. 30 patients were recruited to the study protocol and were randomised into three groups i.e., group I: patients on tab. enalapril + tab. placebo (HS); group II: patients on tab. enalapril + tab. alprazolam (0.5 mg HS) and group III: patients on tab. enalapril + tab. risperidone (0.5 mg HS). The following parameters were analysed after a period of 8 weeks: (a) BP, (b) adverse drug reactions, (c) QOL measures, (d) patient compliance.

Results: A significant drop in systolic blood pressure (SBP) was observed in the risperidone and placebo group as compared to the alprazolam group. There was no treatment withdrawal because of adverse drug reactions. There was no significant change in quality of life (QOL) scores after 8 weeks of adjunctive therapy. Adherence to treatment regimen was > 90%. Magnitude of BP reduction among the three treatment groups after 8 weeks of the study period was similar, though a significant drop in SBP was observed in the risperidone and placebo group.

Conclusion: Adjunctive therapies used in the present study are equally effective as the non-pharmacological lifestyle modifications in vogue, but the balance is to be maintained between the QOL and the therapy selected.

Keywords: Essential hypertension, risperidone, alprazolam.

Introduction

Hypertension (HTN) is the most important non-communicable public health problem in the world[1]. It is a syndrome that comprises of many abnormalities including obesity, abnormal lipid metabolism, insulin resistance, altered glucose metabolism, arterial stiffness, increased sympathetic activity (peripheral or central) and renal disease[2]. Multifactorial causation of essential HTN advocates a wide array of treatment modalities.

ACE-inhibitors have emerged by the very nature of their pharmacological profile, as safe and efficacious antihypertensives, which not only reduce the complications but also improve the quality of life (QOL) of patients. Currently ACE-inhibitors are considered as appropriate first-line therapy for diastolic and/or systolic hypertension[3].

Psychological/emotional stress/anxiety cause temporary increase in BP that in the long-term can contribute to the development of hypertension, which is a well documented fact in animal studies[4, 5]. Lifestyle modifications primarily act by reducing the increased central sympathetic outflow[6]. The use of various non-pharmacological therapies, better termed as lifestyle modifications for the treatment of hypertension has risen markedly in the past few years but yet, there is hesitant attitude of the practitioners to use them and this can be attributed both to lack of evidence in support of these therapies as well as clinicians' difficulty in convincing the patients to adhere to them. As alternatives to lifestyle modifications, efficacious pharmacological adjuncts can be used like alprazolam[7] which targets to reduce the central sympathetic outflow. Studies have demonstrated that the addition of alprazolam to the antihypertensive therapy lead, to a significant reduction in both systolic blood pressure (SBP) and diastolic blood pressure (DBP).

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It has also been noted in epidemiological studies that both environmental[8] and occupational stress[9] increase BP. For this reason, the anti-anxiety drugs, e.g., benzodiazepines (BZPs) are at times prescribed along with the conventional antihypertensives in mild and moderate cases of essential hypertension to undo the increased central sympathetic outflow[10].

Antipsychotics are also known to be used in chronic anxiety disorders and were known at times as major tranquillisers. Fortunately, low-dose of an atypical antipsychotic like risperidone has a low adverse effect profile. Existing evidence indicates both the safety and the efficacy of relatively low-doses of the atypical antipsychotics (like risperidone) as an adjunctive therapy for patients with non-psychotic anxiety disorders. Risperidone has an antagonistic action on 5-HT2$_A$, 5-HT2$_C$, D_2, H_1, α_1 and α_2 receptor sites[11].

Potent α_1 blockade is responsible for orthostatic hypotension which is evident at low doses. This motivated us to use risperidone as an adjunct to the treatment of essential hypertension. The present study was planned to explore the possibility of low-dose of risperidone (2 mg/day) as an alternative to alprazolam as an adjunctive therapy in the management of mild-to-moderate cases of essential hypertension with the ACE-inhibitor enalapril as the principal drug.

Material and methods

The present study was approved earlier by the institutional ethics committee of Himalayan Institute Hospital Trust (HIHT) University, Dehradun. The study was carried-out on 30 patients for a period of one year. Patients attending the cardiology OPD of Himalayan Institute of Medical Sciences, Dehradun, were enrolled in the study.

Inclusion criteria

1. Newly diagnosed patients of mild and moderate essential HTN requiring antihypertensive therapy.
2. Male patients of 21 - 65 years of age were included in the study.

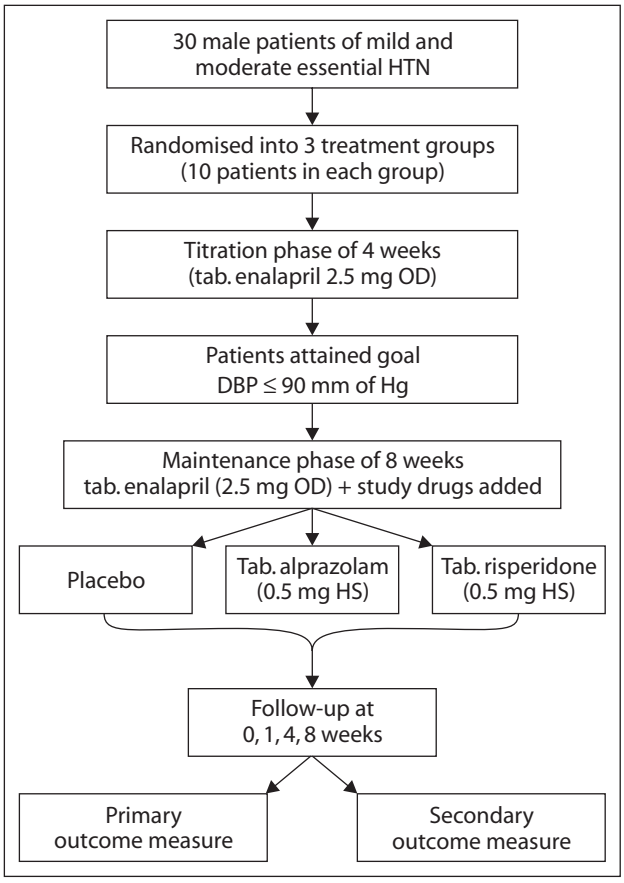
Exclusion criteria

1. Secondary Hypertension
2. Diabetes mellitus
3. Drug treated hypertensives in the past
4. Patients with recent or previous coronary heart disease
5. Patients with psychosis/neurosis.
6. Patients treated with psychopharmacological drugs with history of dyskinesia or neuroleptic syndrome.
7. Patients with history of renal and hepatic dysfunction.

Study design

This was an open label, randomised, comparative trial of alprazolam with low-dose of risperidone in parallel groups of treated mild-to-moderate essential hypertensive patients. Those fulfilling the inclusion criteria were briefed about the trial. Patient information sheets were given to all prospective participants. Written informed consent was obtained from each patient before enrollment in the study. 30 patients were recruited to the study protocol and were randomised into three treatment groups (Table I).

Table I: The study protocol.



Group I: Patients on tab. enalapril (initially 2.5 mg OD and max. tolerated dose, not exceeding 10 mg OD) + placebo.

Group II: Patients on tab. enalapril (initially 2.5 mg OD and max. tolerated dose, not exceeding 10 mg OD) + tab. alprazolam (0.5 mg HS).

Group III: Patients of tab. enalapril (initially 2.5mg OD and max. tolerated dose, not exceeding 10 mg OD) + tab. risperidone (0.5 mg HS).

(2 mg HS was not tolerated by the patients due to non-specific CNS side-effects).

After this randomisation, patients entered into a titration phase of 4 weeks during which enalapril was initiated with 2.5 mg OD so as to attain the goal DBP < 90 mmHg. Patients whose DBP reached the goal on two consecutive visits during the titration phase, entered into a maintenance phase for 8 weeks during which the study drugs were added to the antihypertensive regimen. The placebo group patients were advised various lifestyle modifications like sodium restricted diet, exercise, weight reduction, etc.

BP measurement was done by standard mercury sphygmomanometer with the appropriate sized cuffs at each clinical visit during the titration phase (0, 1st, 2nd, 3rd, 4th weeks) and during the maintenance phase (0, 1st, 2nd, 4th and 8th weeks).

Patients were also assessed for quality of life by using a questionnaire, which was derived, modified, and standardised from the Rand Medical Outcome Study[12]. Based on the response of the questionnaire designed for the purpose, a sum total of all responses were calculated to know the QOL score. A similar assessment was made at the end of the study and was compared with the base line score.

Each patient's compliance (adherence) was determined on the basis of the patient's clinic attendance and pill count. At every visit, patients were given medication for 2 weeks to ensure adherence. The patients were asked to bring along the packet of tablets given to them at the last visit. The number of tablets left were compared with the patient's narration of being regular to the treatment. Thus adherence was estimated. Patient was considered compliant if he had consumed the medication on at least 80% of the days.

Statistical analysis

The primary outcome measure was the rate of treatment success, and the secondary outcome measures were the rate at which the goal BP was achieved during the titration phase and the rate of termination due to adverse reactions. All results have been reported according to an intention-to-treat analysis. Chi-square test of homogeneity was performed to compare the proportion for all categorical responses in the three treatment groups.

Results

The baseline demographic profile of the patients in all study groups was similar except that BMI for the patients in the alprazolam group at baseline was significantly more ($p < 0.05$) than those in the remaining groups. On the other hand the risperidone group comprised of significantly more ($p > 0.05$) number of patients in normal weight category when compared to the alprazolam group (Table II).

The mean age of the patients was 37.1 ± 2.51 years. The distribution of the presenting complaints (headache, fatigue, anxiety, and pain) of the patients across the treatment groups was similar at the baseline.

During the titration phase of 4 weeks in 30 patients before randomisation, the dose of enalapril was titrated to bring DBP ≤ 90 mmHg. The daily dose of enalapril was 3.25 ± 0.38 mg and there was a mean reduction of SBP by 12.33 ± 2.79 mmHg ($p < 0.05$) and DBP by 9.27 ± 1.42 mmHg ($p < 0.05$) (Table III, Fig. 1).

Then the patients were randomised into three treatment groups in the maintenance phase, for 8 weeks of adjunctive therapy, with either placebo, alprazolam or risperidone. The mean fall in BP up to 8 weeks of therapy was observed. The magnitude of reduction in BP irrespective of initial values, after 8 weeks of adjunctive therapy was comparable amongst the three treatment groups. A significant drop of SBP ($p < 0.05$) was observed after 8 weeks of study both in placebo and risperidone group (Table IV, Fig. 2). The magnitude of reduction of DBP after 8 weeks of study period was not significant in either of the three treatment groups.

Table II: Demographic and clinical characteristics of the patients in the three study groups at baseline.

	Treatment groups		
	Enalapril + placebo (n = 10)	**Enalapril + alprazolam (n = 10)**	**Enalapril + risperidone (n = 10)**
Demographic characteristics			
Average age in years	39.9 ± 2.68	37.6 ± 2.68	34 ± 1.48
Average BMI	27.2 ± 0.95	28.5 ± 0.56	24.5 ± 0.93
Clinical characteristics			
Pulse rate	82.6 ± 2.35	84.4 ± 0.63	81.2 ± 2.72
Temp (° F)	98.3 ± 0.16	98.28 ± 0.16	98.3 ± 0.16
History of presenting complaints			
Headache	4	5	4
Anxiety	1	3	2
Palpitation	2	2	0
Fatigue	3	0	4
Family history of hypertension	1	4	1
Alcohol and non-veg. consumption	14	17	14

Table III: Systolic (SBP) and diastolic blood pressure (DBP) recordings in mm of Hg (mean ± SEM) at the beginning (T_0) and after 4 weeks (T_4) of titration (pre-study) period in the 30 patients before randomisation.

Daily dose (in mg) oral enalapril (mean ± SEM) (dosage range: 2.5 - 5 mg)	Parameter measured	SBP and DBP at the beginning of the study T_0	SBP and DBP at 4 weeks of the study period T_4	T_0 minus T_4
3.25±0.38	SBP	143.80±3.50	131.5±1.94*	12.33±2.79
	DBP	96.53±1.34	87.3±1.4**	9.27±1.42

Table IV: Systolic (SBP) and diastolic blood pressure (DBP) recordings in mm of Hg (mean ± SEM) at the beginning (M_0) and after 8 weeks (M_8) of study period in the 3 treatment groups.

Treatment group (n = 10)	Daily dose (mg) of oral enalapril at M_0 (mean ± SEM) (dosage range = 2.5 - 5 mg]*	Parameter measured	Beginning of a study M_0**	After 8 weeks of study M_8***	M_0 minus M_8
Tab. enalapril OD	3.25 ± 0.38	SBP	130.7 ± 1.43	125.1 ± 1.39	5.6 ± 0.89
+ placebo		DBP	86.4 ± 1.93	83.3 ± 1.30	3.4 ± 1.64
Tab. enalapril OD + tab.	3.25 ± 038	SBP	129.8 ± 1.71	127.8 ± 2.32	2 ± 1.55
alprazolam 0.5mg HS		DBP	88.9 ± 1.23	84.6 ± 1.51	3.2 ± 1.47
Tab. enalapril OD + tab.	4 ± 0.40	SBP	130.2 ± 1.16	125.1 ± 1.11	5.6 ± 0.93
risperidone 0.25 - 0.5 mg HS		DBP	87.8 ± 0.89	84.5 ± 1.46	2.8 ± 1.41

Patients treated with placebo had a significant ($p < 0.05$) improvement in QOL over 8 weeks of the study period as compared to risperidone group or alprazolam group (Table V, Fig. 3).

Table V: Quality of life (QOL) scores (mean ± SEM) in the three treatment groups at the beginning (M_0) and after 8 weeks (M_8) of study period.

Treatment group (n = 10)	QOL scores		
	M_0	M_8	M_8 minus M_0
Tab. enalapril 2.5 - 5 mg OD + placebo	37.3 ± 1.58	41.3 ± 1.14	4 ± 0.44
Tab. enalapril 2.5 - 5 mg OD + tab. alprazolam 0.5 mg HS	38.3 ± 1.35	40.3 ± 1.20	1.5 ± 0.47
Tab. enalapril 2.5 - 5 mg OD + tab. risperidone 0.25 - 0.5 mg HS	40.8 ± 1.52	41.4 ± 1.26	0.6 ± 0.43

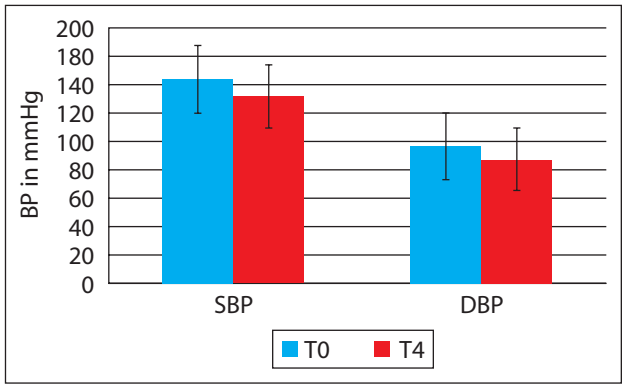


Fig. 1: *Systolic (SBP) and diastolic blood pressure (DBP) recordings in mm of Hg (mean ± SEM) at the beginning (T_0) and after 4 weeks (T_8) of titration (pre-study) period in the 30 patients before randomisation.*

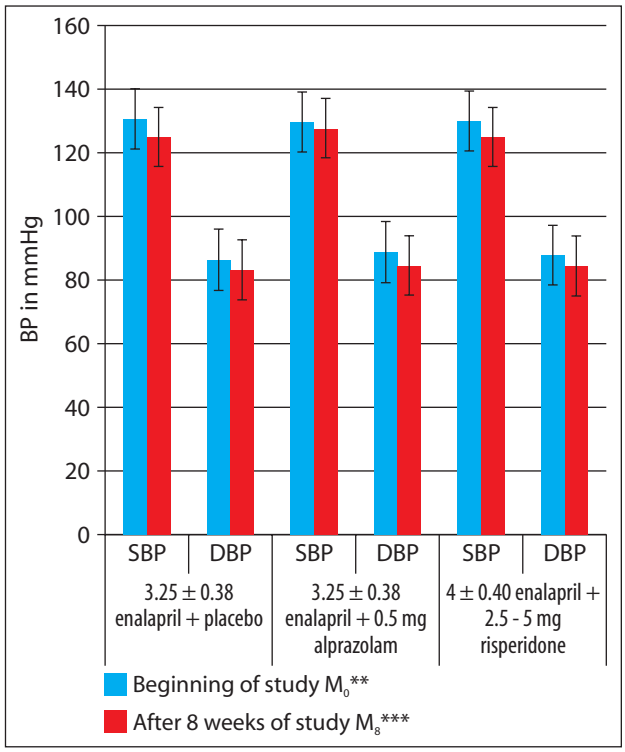


Fig. 2: *Systolic (SBP) and diastolic blood pressure (DBP) recordings in mm of Hg (mean ± SEM) at the beginning (M0) and after 8 weeks (M8) of study period in the 3 treatment groups.*

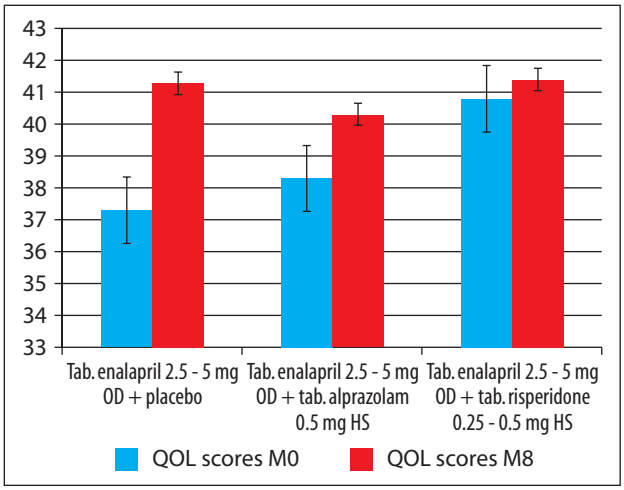


Fig. 3: *Quality of life (QOL) scores (mean ± SEM) in the three treatment groups at the beginning (M_0) and after 8 weeks (M_8) of study period.*

In the present study, adverse reactions did not cause any treatment withdrawal. No drug interactions were reported during the study period. Adherence was excellent in all the groups as the participants took at least 80% of the prescribed regimen.

Discussion

The present paradigm of management of essential hypertension focuses on early target oriented and adequate treatment which is consistent with patient's safety, quality of life (QOL) and cost effectiveness as well.

In the present study, we recruited 30 male patients who were aged between 21 - 65 years (mean age 37.1 ± 2.51 years) at baseline.

The present study demonstrated that all patients achieved and maintained the goal BP during the study period at the average daily dose of 3.25 ± 0.38 mg of oral enalapril. In the present study, the BP of all the patients was brought down to desired levels at a much lower average dose.

There was a steep fall in mean BP over the first 2 weeks which then continued more gradually for the rest of the study period.

This course of BP reduction over a period of time appears to be similar to that observed in the MRC trial[13]. Although this study was limited to male patients, it provided some information about the comparative efficacy of commonly used short-term adjunctive drug treatment with alprazolam against risperidone and placebo for the treatment of mild-to-moderate cases of essential hypertension with enalapril as the principal drug. The time of administration of study medication (at bed time) was selected so as to ensure compliance and tolerability of the drugs used. The inclusion of placebo group allowed the true estimate of the active adjuvant drug effects.

In the present study, a significant reduction in SBP (Table III) was achieved in the placebo and risperidone group as compared to the alprazolam group. The maximum drop in SBP and DBP after 8 weeks of adjunctive therapy was 5.6 ± 0.93 and 3.4 ± 1.64 mmHg respectively for the placebo group (Table III). This magnitude of reduction achieved in the present study during the maintenance phase is less than that reported in TOMHS study[14] where comparison was made between combination of antihypertensive drug and nutritional hygiene therapy versus nutritional hygiene intervention alone. The findings of the present study when compared to TOMHS study were different, perhaps because of the 4 weeks titration phase with enalapril treatment that had already shown a drop in both SBP and DBP of 12.3± 2.79 and 9.27 ± 1.42 mmHg respectively. The magnitude of antihypertensive effect of enalapril used during the titration phase could have eclipsed the otherwise appreciable drop in BP that might have occurred because of the adjunctive therapy *per se*.

In the present study, it was expected that risperidone and alprazolam by the virtue of their ability to decrease the central sympathetic outflow would cause significant reduction in BP. But results showed that alprazolam could not achieve a significant decrease in SBP like that of placebo or risperidone. This insignificant drop in SBP over eight weeks study period in the alprazolam groups may be attributable to significantly greater mean BMI in that group. The alprazolam group also showed a trend of positive family history, though not significant. Alcohol consumption[15] and non-vegetarian diet[16] are known risk factors for hypertension. Their marginally greater number in the alprazolam group might be reflecting in interpretation of the present study, that the alprazolam group showed significantly lesser drop in SBP over eight weeks of the study period. Most of the studies done in the past, reviewing the effects of lifestyle modifications like sodium restricted diet[17], weight reduction[18], cognitive behavioural techniques[19], and omega fatty acid rich diet[16] on hypertension reveal that an average drop of 5 - 6 mmHg and 2 - 3 mmHg is achieved in SBP and DBP respectively. Our results bear similarity with these findings. Adjunctive therapies used in the present study are equally effective as the non-pharmacological lifestyle modifications in vogue. There was no treatment withdrawal because of adverse drug reactions. The dose of risperidone used in the study was 0.25 - 0.5 mg and perhaps significant reduction in BP could be achieved if dose was increased to 2 mg, but then the possibility of having a not so good ADR profile cannot be ruled-out. Low-dose (0.5 mg) alprazolam for 8 weeks does not cause any drug dependence. Studies have reported that most persistent alprazolam use does not represent abuse or addiction as usually understood[20]. There is no risk of drug dependence with risperidone instead it has been used for the treatment of substance abuse like cocaine[21].

It was anticipated that alprazolam and risperidone, by the nature of their known pharmacological action on benzodiazepine receptor (BZP receptor) and 5-HT receptor respectively, and hence having appreciable anxiolytic effect, will improve the QOL of the patients; but on the contrary, both worsened the QOL of the patients after 8 weeks of treatment. The scale used in the present study was more sensitive than used by Brook *et al*[22] that fetched clinically relevant results. Also unexpected results could be because of the shorter duration of the study period and the smaller sample size. In clinical practice, the QOL aspect needs to be balanced against the effectiveness of the drug selected. In an ideal drug regimen, the demands for maintenance of the QOL and for therapeutic effectiveness can be reconciled.

The non-pharmacological therapy of various lifestyle modifications act as an adjunctive therapy for the control

of hypertension with an advantage that it provides a better QOL to the patient. But clinicians have difficulty convincing their patients for the same. Under such conditions, anxiolytic drugs like alprazolam and risperidone can act as adjuncts in the treatment of hypertension. The problem with using adjunctive treatment is that it may compromise the QOL of the patient. In clinical practice, the QOL aspects have to be balanced against the effectiveness of the drug selected.

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ORIGINAL ARTICLE

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A Study on the Modulation of Adenosine Deaminase (ADA) Activity in Monocytes of Type 2 Diabetic Patients by Antioxidants

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Abstract

Purpose: To access the oxidative stress in type 2 diabetic mellitus, by measuring the adenosine deaminase (ADA) levels in serum, co-cultured monocyte, monocyte supernatant and to verify the modularity effect of antioxidant on ADA levels.

Material and methods: Adenosine activity was measured in the serum, 24 hours co-cultured monocyte and cell free supernatant of the monocyte in 50 type 2 diabetic subjects. 20 age and sex matched healthy subjects were taken as controls. The ADA activity was reassessed after treating the co-cultured monocytes with antioxidants namely, N-AcetylCysteine and Epigallocatechin – 3 – gallate (EGCG).

Results: Adenosine deaminase levels were found to be raised in monocytes of type 2 diabetic patients. This level decreased after antioxidant therapy.

Conclusion: Adenosine deaminase activity could be regarded as a strong indicator of reactive oxygen species (ROS) production due to oxidative stress in type 2 diabetic subjects, which could be modulated by antioxidants.

Key Words: N-AcetylCysteine, epigallocatechin – 3 – gallate, reactive oxygen species, reactive nitrogen species (ROS), adenosine deaminase (ADA).

Introduction

The increasing prevalence of type 2 diabetes in the Indian subcontinent makes it important to recognise, postpone, or even prevent the serious complications associated with it, if possible. The oxidative stress resulting in free radical production [reactive oxygen species (ROS) and reactive nitrogen species (NOS)] which is considered to be a common pathogenic factor leading to insulin-resistance, β-cell dysfunction and ultimately type 2 DM[1], is also considered as an underlying cause of both the macrovascular as well as microvascular complications[2]. Among the well-known effects of adenosine are selective regulation of pro- and anti-inflammatory cytokines released and free radical production[3,4,5]. Increased level of adenosine deaminase in diabetic patients could result in increase in hypoxanthine which oxidizes xanthine into uric acid and concomitant generation of O_2. Several studies have found elevated ADA activity in subjects with type 2 DM[6,7,8]. The present study was performed in order to estimate the ADA levels in serum, monocytes and in monocyte supernatant in type 2 diabetic subjects and also to look for any effect on ADA levels after modulating the same co-cultured monocytes by antioxidants.

Material and methods

The study was conducted in the Endocrine division, Department of Medicine, JN Medical College, AMU, Aligarh. 50 subjects of type 2 diabetes mellitus were included in the study. Their demographic profile with biochemical characteristics was estimated. Peripheral blood monocyte cells (5×10^6 cells/well) were added in 12 wells tissue culture plates in complete RPMI-1640 medium and subsequently incubated at 37°, 5% CO2 for 1 - 2 hours. The cells were washed, adhered with 2% autologous serum followed by overnight resting. ADA levels in serum, co-cultured monocytes, monocyte supernatant were evaluated and compared with 20 age and sex matched healthy controls. Statistical analysis was performed using SPSS version 10 statistical package for windows (SPSS, Chicago, Illinois, USA). Continuous variables were expressed as mean ± SD (Gaussian distribution) or range. Unpaired and paired student t test for independent and dependent samples were used in comparing continuous data between two groups. All p values were two-tailed and values of < 0.05

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were considered to indicate statistical significance. All confidence intervals were calculated at 95% level. Pearson's correlation of ADA activity with clinical, and biochemical variables were estimated. Multistage linear regression analysis using ADA activity on dependent variable (HbA_{1C} alone and HbA_{1C} + fasting blood sugar) in same subjects was performed. Thereafter, the above adherent monocytes were co-cultured with varying doses of N-AcetylCysteine (10 Mm) and EGCG (5 µg/ml) for 24 hours. Cultures were then harvested after 24 hours and cells were lysed in 0.5 ml of Trizol reagent (invitrogen Inc., Carlsband, CA, USA) and stored at -70°. Finally, modularity effects of these antioxidants on the same co-cultured monocytes and their supernatant was evaluated by re-evaluating ADA levels.

Observations and results

Of the 50 type 2 diabetic subjects included in the study, 36 were males while the rest were females. In the control group, out of 20, 14 were males. Age in the study group was 52.19 ± 8.04 while in the control group it was 49.5 ± 7.65. HbA_{1C} in the study group was 8.55% while it was 5.02% in the control group. Serum ADA levels in the study group reveal value of 31.72 ± 2.80 U/l while in the control group it was 19.13 U/l with t value of -18.53 and p value of < 0.01. Monocyte ADA values in study group was 22.74 ± 2.8 U/l while in control it was 9.26 ± 2.81U/l with a p value of < 0.01. The Monocytes supernatant showed the same trends (Table I). Pearson's correlation of ADA activity showed ADA activity significantly correlated with hyperglycaemic parameters like Hb_{A1C} ($p < 0.01$) fasting blood sugar ($p < 0.05$) and post-prandial blood sugar ($p < 0.05$). ADA activity was not significantly correlated with age, BMI, RFT, or serum lipid levels (Table II).

Table II: Pearson's correlation of ADA activity with clinical and biochemical variables in patients of type 2 diabetes mellitus.

	Pearson's Correlation	Sig. (2-tailed)
Age (years)	0.208	NS
BMI (kg/m2)	.177	NS
BS (f)	.314*	.027
BS (pp)	.310*	.028
HbA_{1c} (%)	.688**	.000
B. Urea (mg%)	.045	NS
S. Creatinine (mg%)	.091	NS
Total cholestrol (mg%)	.260	NS
HDL (mg%)	-.072	NS
LDL (mg%)	.155	NS
TG (mg%)	.201	NS
VLDL (mg%)	.202	NS
ADA (monocyte)	1.000**	.000
ADA (M. supernatant)	1.000**	.000

*** Correlation is significant at the 0.01 level (2-tailed).*
** Correlation is significant at the 0.05 level (2-tailed).*
NS = not significant.

On performing multistep regression, HbA_{1C} entered as the most important significant variable with a value of regression value of 0.688, indicating appropriate predictability in the relationship between the dependent (ADA activity) and independent (HbA_{1C}) variables. R^2 value (0.474) indicates the extent to which HbA_{1C} accounts for the total variance in mean ADA activity. In our case it was 47%. β indicates the nature and dynamics of the relationship between the two variables.

Table I: ADA Levels in control and study group.

	Control		Type 2 diabetes		t	p
	mean	SD	mean	SD		
ADA (serum)* (U/l)	19.13	1.82	31.72	2.80	-18.53	< 0.01
ADA (monocyte)** (U/l)	9.26	1.31	22.74	2.81	-20.56	< 0.01
ADA (M. supernatant)*** (U/l)	7.06	1.31	18.84	2.79	-17.97	< 0.01

** ADA level in serum*
*** ADA level in 24-hour monocytes culture*
**** ADA level in cell-free supernatant of 24-hour monocyte culture*
p-value indicates difference (independent sample t-test). T is the value of student 't' test

Furthermore, it was seen that each unit increase in the level of HbA_{1C} increased the level of ADA by 0.688 units (provided all other independent variables are kept constant). The t value indicates the significance of regression and the slope of regression line. In our case the regression value is significant, β value is significantly different from zero and the regression line was having a significant slope in comparison to the x-axis. The confidence intervals for β showed that our findings are true to the entire population from which the sample has been taken.

Fasting blood sugar entered as the second most important significant variable. The model 2 contains two variables, HbA_{1C} and fasting blood sugar. Regression value for model 2 was 0.721 thereby indicating that the variables had a predictive power of 72%. And the R^2 value was 0.520 which denoted that the variables in model 2 (HbA_{1C} and fasting blood sugar) account for 52% variation in the level of the dependant variable, ADA. β indicated the nature and dynamics of relationship between two variables. Thus, in model 2 the most powerful predictor of ADA value was HbA_{1C} ($\beta = 0.889, t = 6.426, p < 0.001$), followed by fasting blood sugar ($\beta = -0.294, t = -2.125, p < 0.05$). Regression value was significant, β value was significantly different from zero and the regression line had a significant slope in comparison to the x-axis. Confidence intervals for β showed that our findings are true to the entire population from which the sample has been taken (Table III). Finally after washing with RPMI-1640 media, monocytes were co-cultured with 5 µg/ml of EGCG and 10 Mm NAC for 24 hours. The ADA values were compared with those prior to antioxidants addition. With EGCG, the p value came out to be < 0.001, while with NAC also, the p value came out to be p < 0.001. Again on comparing the two antioxidants p value came out to be < 0.001 (Table 4).

Table IV: Comparing the modultory effect of NAC versus a natural antioxidant, EGCG.

	With NAC (10 Mm)		With EGCG (5 G/NK)		t	Sig. (2 tailed) p
	Mean	SD	Mean	SD		
ADA level in monocyte (U/l)	11.88	1.63	10.06	1.17	22.107	< 0.001
ADA level in monocyte supernatant (U/l)	8.98	1.63	6.96	1.17	24.107	< 0.001

Discussion

Increased levels of adenosine in diabetic cells accompanied by decreased activity of adenosine kinase, diminished efflux, may drive the metabolism of adenosine towards deamination by adenosine deaminase (ADA) to inosine and hypoxanthine; the latter product serves as a substrate for xanthine oxidase which oxidizes xanthine into uric acid with concomitant increased generation of O_2^-. It has been demonstrated that increased purine degradation results in altered free radical formation[9,10]. ADA is a marker of T-cell activation and is related to the production of ROS by neutrophils[11], the central mechanism of oxidative damage in diabetes. In addition, a link between the ADA gene locus and maturity onset diabetes of the young (MODY) has also been reported[12]. In the present study, we found significantly elevated levels of serum ADA in subjects with type 2 DM with a mean ADA level of 31.72 ± 2.80 U/l. The study also found a Pearson's correlation between the mean ADA activity and hyperglycaemic parameters like Hb_{A1c} ($p < 0.01$), fasting blood sugar ($p < 0.05$) and post-prandial blood sugar ($p < 0.05$).

Among these, HbA_{1c} has the strongest production power for ADA activity with regression value of 0.68 and when

Table III: Multistep regression model.

Model	Variables	R	R^2	β	t	p	95% confidence interval for β	
							Lower	Upper
1.	HbA_{1C}	0.688	0.474	0.688	6.576	0.000	0.860	1.618
2.	HbA_{1C}	0.721	0.520	0.889	6.426	0.000	1.100	2.102
	Fasting blood sugar			-0.294	-2.125	0.039	-0.031	-0.001

1. *Predectors: (constant), HbA_{1c} (%)*
2. *Predictors: (Constant), HbA_{1c} (%), BS*

combined with fasting blood sugar the regression value measured to 0.72. HbA_{1c} alone is responsible for 47% variance in ADA. Our findings are consistent with two studies by Kurtul *et al*[8] who reported that ADA activity was significantly raised in poorly controlled diabetics with HbA1c > 7%. Hoshino *et al*[6] had previously reported that poorly controlled type 2 DM patients had mean HbA1c > 8.5% while in controlled diabetes patients this level was < 7%.

Conclusion

Adenosine deaminase activity is elevated in serum and in monocytes of patients with type 2 diabetes mellitus. Adding antioxidants N-acetylcysteine or Epigallocatechin-3-gallate reduces ADA levels and thereby the oxidative stress, which could delay the complications associated with diabetics.

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REVIEW ARTICLE

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Cardiac Biomarkers: When to Test? – Physician Perspective

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Introduction

A biomarker is a substance used as an indicator of a biologic state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention. In a patient having a triad of chest pain, ECG changes, and elevation of cardiac biomarkers while chest pain is highly variable and subjective, ECG and the biomarker abnormality lend objectivity to help define the diagnosis of acute coronary syndrome (ACS) or acute myocardial infarction (AMI).

What are they?

Cardiac biomakers are substances that get released into the blood when the heart is damaged. Cardiac biomarkers can be detected in blood by a specialised immunoassay. They are used to help diagnosis, evaluate, and monitor patients with suspected acute coronary syndrome (ACS).

Cardiac biomarkers are not necessary for the diagnosis of patients who present with ischaemic chest pain and diagnostic ECG with ST segment elevation. But cardiac biomarkers are very useful in patients of non-diagnostic ECG. The patients with ischaemic chest pain and diagnostic ECG with ST segment elevation may be candidates for thrombolytic therapy or primary angioplasty. Treatment should not be delayed to wait for cardiac marker results, especially since the sensitivity is low in the first 6 hours after symptom onset.

The most common cardiac biomarkers used in the evaluation of acute coronary syndrome are troponin T and I , CK-MB, myoglobins. Out of these troponin T and I are the markers of choice for detecting the heart damage. However, other cardiac biomarkers are less specific for heart and may be elevated in other conditions like severe muscle injury, liver disease, and kidney disease. Many other potential cardiac biomarkers are being researched but their clinical utility has yet to be established.

Cardiac biomarker tests must be available to the doctor 24 hours a day, 7 days a week with rapid turn-around time of one hour[2]. Some of these tests may be performed in the emergency room or at the patient's bedside. Furthermore, the introduction of newer cardiac troponin assays with increased sensitivity and lower cut-off levels have rendered traditional early markers such as myoglobin and CK-MB isoforms unnecessary for early diagnosis of myocardial infarction[3,4,5].

Usefulness of cardiac biomarkers

1. Diagnosis of acute myocardial infarction/acute coronary syndrome by detecting myocardial damage.
2. Prognostic value and risk stratification of:
   - Patients with acute coronary syndrome.
   - Patients undergoing pre- and post-reperfusion/ coronary interventions.
   - Patients with congestive heart failure, renal disease, etc.

Types of cardiac biomarkers

1. Cardiac troponin I and T
2. CK-MB
3. Myoglobin
4. BNP
5. hs-CRP
6. Myeloperoxidase
7. Ischaemia modified albumin.

Cardiac troponins

The cardiac troponins regulate the interactions of actin and myosin and are more cardiac specific than CK-MB. The

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cardiac troponin complex consist 3 subunits: TnT, TnI and troponin C (Tn C). Monoclonal antibody based immunoassays have been developed to detect cardiac-specific TnT and cardiac specific TnI, because the amino-acid sequences of skeletal and cardiac isoforms of both TnT and TnI have sufficient dissimilarity. But troponin C has amino acid sequences similar to those of skeletal and cardiac isoform, so that no immunoassays have been developed for chemical purposes. Therefore, the term "cardiac troponin" refers to either TnT or TnI or to both. Cardiac troponins are used mainly to aid in the diagnosis of chest pain patients with non-diagnostic ECG; they are also used as prognostic indicators of a MI and to identify patients having an increased risk from cardiac events resulting in death[6].

Laboratory range definitions

(a) Cut-off is at 99th percentage of normal reference population.

(b) Cardiac troponin levels are undetectable in normal subjects, this 99th percentile corresponds to < 0.06.

(c) Heparin in sample can result in lowered value.

Troponin levels begin to rise 3 - 4 hours after the onset of acute coronary syndrome, and roughly 80% of patients with ACS will have a positive value at 3 hours. These levels remain elevated for 7 to 10 days. There is a direct relationship between the degree of elevation of troponin value and long-term outcome after episode of acute coronary syndrome[7,8].

Troponin T level

Level less than < 0.07 mg/ml: Negative.

Level 0.07 to 0.5 mg/ml: consistent with possible cardiac damage and possible increased clinical risk.

Level > 0.5 mg/ml: consistent with cardiac damage and increased clinical risk.

Cardiac troponins are sensitive, specific, and provide prognostic information for patients with ACS. Therefore, troponins are currently the cardiac markers of choice for patients with ACS. They also have greater sensitivity for smaller degree of myocardial damage than detectable by CK-MB assays[9]. In patients with clinical history suggestive of ACS, even slight elevations of TnI and TnT can identify patients with increased risk of complications who could potentially benefit from aggressive management strategies like Gp II b/IIIa administration and/or coronary interventions[10]. Apart from ACS, troponin levels are also increased in same causes such as:

1. Pulmonary embolus
2. Myocarditis
3. Cardiac contusion
4. Congestive cardiac failure
5. Cardioversion or radiofrequency ablation
6. Septic shock
7. Chemotherapy (adriamycin, 5-fluorouracil)
8. Renal failure
9. Hypothyroidism

Creatine kinase (CK)

Creatine kinase is an enzyme responsible for transferring a phosphate group from ATP to creatine. It is composed of M and B subunits that form CK-MM, CK-MB and CK-BB isoenzymes. Total CK is not cardiac specific but CK-MB is a sensitive as well as a specific marker for myocardial infarction. CK-MB begin to rise 4 - 6 hour after myocardial infarction, peak at 24 hours and return to normal within 48 - 72 hours. CK-MB estimation is useful not only for diagnosis of MI but also for the diagnosis of reinfarction.

Relative index

The formula for calculation of the relative index ratio is: CK-MB/total CK x 100.

Relative index is helpful in differentiating false-positive elevation of CK-MB arising from skeletal muscle. A ratio less than 3 is consistent with skeletal muscle source. Ratio greater than 5 is indicative of cardiac source, and a ratio between 3 and 5 represents a gray zone. The diagnosis of myocardial infarction must not be based on an elevated relative index alone. The relative index may be elevated in clinical settings when either the total CK or the CK-MB is within normal limits. The relative index is only clinically useful when both the total CK and the CK-MB levels are increased[11]. Relative index improves specificity of CK-MB elevation for myocardial infarction.

CK-MB isoforms

The CK-MB isoenzymes exists as two isoforms: CK-MB1 and CK-MB2. CK-MB2 is the tissue form and initially is released from myocardium after myocardial infarction. It is converted peripherally in serum to the CK-MB1 isoforms. The ratio of CK-MB2/CK-MB1 is calculated. Normally the tissue CK-MB1 isoform predominates, so the normal ratio is < 1. A result is positive if CK-MB2 is elevated and ratio is more than 1.7. CK-MB2 is detected in serum within 2 - 4 hours after onset of symptoms and peaks at 6 - 9 hours, so it is used as an early marker for myocardial infarction. It has a sensitivity of 92% at 6 hours after symptom onset compared with 66% for CK-MB[12].

Causes other than ACS of false-positive CK-MB

1. Significant skeletal injury
2. Myocarditis
3. Blunt chest trauma
4. Cardiac catheterisation
5. Shock
6. Cardiac surgery
7. Post-cardio-pulmonary resuscitation

Cardiac markers in CRF

(a) Troponin

A very high prevalence (30 - 70%) of TnT positive results have been reported in asymptomatic patients with CRF who are on dialysis. TnI is also elevated in CRF but less frequently (5%). Hence TnI has more specificity for diagnosis of acute myocardial infarction than TnT in the setting of CRF.

(b) CK-MB

About 30 - 50% of renal failure patients exhibit an elevation in the MB fraction (> 5%) without evidence of myocardial ischaemia. Unlike troponin, CK-MB however is dialysable, and levels are decreased after dialysis.

Myoglobin

Myoglobin is an oxygen storing protein found in skeletal and cardiac muscle. It is released into circulation as early as one hour after myocardial injury. Myoglobin typically rises 2 - 4 hours after onset of myocardial injury, peaks at 8 - 12 hours and returns to normal within 24 hours. Thus, myoglobin is the earliest marker but it lacks cardiac specificity.

Myoglobin should not be used alone as a method for diagnosing myocardial infarction but it should be supplemented with more cardiac-specific markers such as troponin I or troponin T[13,14]. Serial sampling every 1 - 2 hours can increase the sensitivity and specificity.

Table I summarises the currently used cardiac markers.

Emerging cardiac markers

1. hs-C-reactive protein (hs-CRP)

CRP is a non-specific marker of inflammation, and is considered to be directly involved in coronary plaque atherogenesis. CRP is a useful prognostic indicator in patients with ACS. Elevated CRP levels are an independent predictor of cardiac death, AMI, and CHF. Measurement of hs-CRP should be done in the fasting or non-fasting state in metabolically stable patients free of infection or acute illness. The cut-offs for hs-CRP using standardised assays categorises patients as follows:

Low-risk: < 1.0 mg/l

Average risk: 1.0 - 3.0 mg/l

High-risk: > 3.0 mg/l

Very high-risk: > 10 mg/l

Levels of hs-CRP greater than 3 mg/l also predict recurrent coronary events, thrombotic complications after angioplasty, poor outcome in the setting of unstable angina, and vascular complications after by-pass surgery (CABG). Additionally, hs-CRP has prognostic usefulness in cases of acute ischaemia, even without troponin level elevation, suggesting that an enhanced inflammatory response at the time of hospital admission can determine subsequent plaque rupture. These findings explain why individuals with elevated hs-CRP levels are more likely to benefit from aggressive interventions compared to those with low hs-CRP levels[15]. hs-CRP levels correlate only modestly with underlying atherosclerotic disease, but indicate an increased propensity for plaque disruption and/or thrombosis.

Table I: Currently used cardiac biomarkers.

Marker	What it is	Tissue source	Reason for increase	Time to increase	Time back to normal	When/how used
Cardiac troponin	Regulatory protein complex, two cardiac specific isoforms: T and I	Heart	Injury to heart	3 to 4 hours after injury	Remains elevated for 7 to 10 days	To diagnose myocardial infarction, assess degree of damage
CK-MB	Myocardium related isoenzymes of CK	Heart primarily, but also skeletal muscle	Injury to heart and skeletal muscle cells	4 to 6 hours after heart, muscle injury; peak at 24 hour	Returns to normal within 48 - 72 hour	Less specific than troponin, may be ordered when troponin is not available; also used to diagnose re-infarction
Myoglobin	Oxygen storing protein	Heart and skeletal muscle	Injury to heart and skeletal muscle	2 - 4 hours after injury peak in 8 - 12 hrs	Returns to normal within 24 hours	Sometimes, in addition to troponin to provide early diagnosis

2. B type natriuretic peptide (BNP)

BNP is secreted by right and left ventricular myocytes and released in response to stretch, volume overload, and elevated filling pressures. Serum levels of BNP are elevated in patients with asymptomatic LV dysfunction as well as symptomatic HF. The presence of acute heart failure (HP) in patients with ACS is a well known predictor of adverse cardiac events[16]. Therefore it is not surprising that an elevated BNP level is a marker of CHF and is also a predictor of adverse cardiac events in patients with ACS[17]. In addition, the severity of ischaemia is directly proportional to elevation in BNP. A serum BNP of < 100 pg/ml has a good negative predictive value and typically excludes HF as primary diagnosis in dyspnoeic patients. BNP levels correlate with the severity of HF and predict survival[18].

3. Myeloperoxidase (MPD)

Myeloperoxidase is a leukocyte enzyme that generates reactant oxidant species and has been linked to prothrombotic oxidised lipid production, plaque instability, lipid-laden soft plaque creation and vasoconstriction from nitrous oxide depletion. Elevated MPD levels independently predicted the increased risk of major adverse cardiac events including MI, reinfarction, need for revascularisation, or death at 30 days and 6 months, even among those with negative cardiac troponin I and T[19]. Myeloperoxidase may be a useful early marker in the emergency department (ED) based on its ability to detect plaque vulnerability that precedes acute coronary syndrome.

4 Ischaemic modified albumin (IMA)

IMA is a novel marker of ischaemia produced when circulating serum albumin contacts ischaemic heart disease. IMA can be measured by albumin cobalt binding assay that is based on ischaemic modified albumin inability to bind to cobalt. This assay has received the FDA approval for use with troponin and ECG. It is not widely available but may become useful some day for identifying patients at higher risk of ACS. In a recent metaanalysis, this test has high sensitivity and negative predictive value of IMA for detecting ACS especially in combination with troponin and ECG measurements[20], but specificity is very poor[21].

However, IMA level is also increased in patients with liver cirrhosis. Certain infections, and advanced cancer within reduces the specificity of this assay further.

Which is the best cardiac biomarker?

The best marker depends on the time taken to give positive results from onset of symptoms. The earliest markers are myoglobin and CK-MB isoforms. CK-MB and troponins are ideal markers in the intermediate period of 6 to 24 hours. It is important that the clinicians realise that troponins are not early markers. Only 35% of patients with NSTEMI (non-ST elevation myocardial infarction) have positive troponins at baseline evaluation.

Time schedule for cardiac biomarker testing

The sample time at 3 - 4 hours is useful in the chest pain observation unit where rapid triage and early diagnosis are essential. In other patients admitted for ACS, biomarkers drawn at the 3 to 4 hours time interval are not as important as the 6 to 9 hours sample. The recent ACC/AHA guidelines for the treatment of patients with unstable angina and NSTEMI recommend a baseline

sample upon ED arrival and a repeat sample 6 - 9 hours after presentation. Serial sampling that become positive in the 12 to 24 hours time window are unlikely unless the patient has ongoing symptoms of ischaemia after admission. AMI can essentially be ruled-out in patients with negative serial marker results through the 6 - 9 hours period after presentation. This later recommendation from the ACC/AHA guidelines represents a significant change in the standard of care for ruling-out AMI[1,22].

The following table outlines the recommended sampling frequency after ED admission for various cardiac markers.

Table II: Cardiac marker sampling frequency.

	Baseline	3-4 hr	6-9 hr	12-24 hr	> 24 hr
CK-MB isoform, myoglobin	✓	✓	✓		
CK-MB, TnI, TnT	✓	✓	✓	✓ (only if very high-risk)	
Late presenters					✓

Conclusion

Cardiac biomarkers are released into the blood stream after myocardial injury or during pressure or volume overload and myocardial dysfunction. They play an important role not only in the diagnosis of patients of acute myocardial infarction/acute coronary syndrome but also for risk stratification and prognostication of such patients. However, abnormal values should be interpreted carefully in the proper clinical contest.

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REVIEW ARTICLE

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Role of Antioxidants in Hypertension

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Introduction

Hypertension (HT) is a major health problem worldwide. Individuals with hypertension are at an increased risk for stroke, heart disease, and kidney failure. Although the aetiology of essential hypertension has a genetic component, lifestyle factors such as diet play an important role. Excess of sugar and salt or deficiencies of antioxidant vitamins in diet play a vital role in the aetiology of hypertension.

The relationship between hypertension, oxidative stress and antioxidants is complex and inadequately understood. Oxidative stress may play a role in the pathophysiology of hypertension. Human and animal studies have demonstrated that HT is accompanied by increase in oxidative stress. However, the evidence for this in humans is not definitive[1].

Studies demonstrate that hypertension may develop as a result of increased reactive oxygen species[2-8] and that a variety of antioxidant therapies ameliorate hypertension.

Hypertensive effects of oxidative stress are mostly due to endothelial dysfunction resulting from disturbances of vasodilator systems, particularly degradation of nitric oxide (NO) by oxygen-free radicals[9-11].

By altering the balance in the endothelium between vasoconstrictors such as thromboxane and isoprostanes and vasodilators such as nitric oxide, reactive oxygen species contribute to endothelium-dependent vasoconstriction and increased vascular resistance. Oxidative stress raises blood pressure by promoting functional nitric oxide deficiency (through NO inactivation and tetrahydrobiopterin depletion) and by augmenting arachidonic acid oxidation and formation of vasoconstrictive prostaglandin $F_{2\alpha}$.

Reactive oxygen species (ROS) producing enzymes involved in increased oxidative stress within vascular tissue include NADPH oxidase, xanthine oxidase, and mitochondrial superoxide producing enzymes. Superoxide produced by the NADPH oxidase may react with NO, thereby stimulating the production of the NO/superoxide reaction product peroxynitrite. Peroxynitrite in turn has been shown to uncouple eNOS, therefore switching an anti-atherosclerotic NO producing enzyme to an enzyme that can accelerate atherosclerosis by producing superoxide. Increased oxidative stress in the vasculature is not restricted to the endothelium and also occurs within the smooth muscle cell layer.

Increased peripheral vascular resistance is an important contributor to the pathogenesis of hypertension. Elevated total peripheral vascular resistance is ascribed to dysregulation of vasomotor function and structural remodelling of blood vessels.

Many studies have suggested that the intracellular calcium concentration, which regulates vasomotor function, is controlled by free radicals and redox signalling, including NAD(P)H and glutathione (GSH) redox. Key targets that control intracellular calcium concentration such as ion channels, Ca^{2+} release from internal stores and uptake by the sarcoplasmic reticulum, are regulated by changes in intracellular redox and oxidants. Reactive oxygen species increase vascular tone by influencing the regulatory role of endothelium and by direct effects on the contractility of vascular smooth muscle. ROS contribute to vascular remodelling by influencing phenotype modulation of vascular smooth muscle cells, aberrant growth and death of vascular cells, cell migration, and extracellular matrix (ECM) reorganisation. Thus, there are diverse roles of the vascular redox system in hypertension. The thioredoxin (TRX) system is active in the vessel wall and functions as an important endogenous antioxidant. This system consists of TRX, TRX reductase, and NAD(P)H, and is able to reduce reactive oxygen species through interactions with the redox-active centre of TRX. Among the TRX

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superfamily is peroxiredoxin (PRX), a family of non-haeme peroxidases that catalyses the reduction of hydroperoxides into water and alcohol. Recent evidence implicates TRX in cardiovascular disease associated with oxidative stress, such as hypertension. Thioredoxin activity is influenced by many mechanisms, including transcription, protein-protein interaction, and post-translational modification. Regulation of TRX in hypertensive models seems to be related to oxidative stress. In addition, oxidative stress in the kidney may be involved in the pathogenesis of salt retention and hypertension. Antioxidants can restore endothelial function and decrease blood pressure as reported in some studies on hypertension.

Hypertension, on the other hand, may lead to tissue damage through lipid peroxidation and other oxidative mechanisms[12]. *In vivo* oxidation of low-density lipoproteins by oxygen-free radicals may increase hypertension-related atherogenesis, and antioxidants may be beneficial in this regard. Studies concerning associations between serum levels of antioxidants and hypertension have been inconsistent.

Hypertension impairs myocardial microvascular function and integrity. It is associated with impaired coronary endothelial function and can impair myocardial perfusion. One of the mechanisms that might be responsible for HT-induced myocardial dysfunction is an increase in oxidative stress. HT has been shown to impair the function of both the vascular endothelium[13-14] and smooth muscle layers. Increases in arterial blood pressure induce proliferation of vascular smooth muscle cells and change their phenotype and conductance of calcium[15]. The vascular endothelium functions as a barrier, maintains homoeostasis, and has anticoagulant and anti-inflammatory properties. HT is associated with alterations in mean arterial pressure (MAP), which might reflect impaired function of the endothelium. It is possible that antioxidant vitamins might improve some of the deleterious effects of oxidative stress (e.g., endothelial function, lipid peroxidation, tissue injury)[16], but might not succeed in reversing the deleterious effect of HT on other aspects (e.g., vascular remodelling, vascular smooth muscle cell function, or nervous system activity). In several studies, antioxidant intervention did reduce blood pressures in HT[17-18]. Differences in the effect of antioxidants on blood pressure may be attributed to different doses, routes of administration, or timing and type of antioxidant intervention[19-21]. Blockade of oxidative stress might have significant implications in atherosclerosis.

Review of literature

The Dietary Approaches to Stop Hypertension (DASH) studies showed that diet rich in fruits, vegetables, low fat dairy products, whole grains, nuts, and deficient in salt and sugar helps to reduce blood pressure. Supplementation with antioxidants, including vitamin C, E, or B_6, thiols such as lipoic acid and cysteine, and the quinone enzyme Q10, have been shown to lower blood pressure in animal models and humans with essential hypertension. These antioxidants may achieve their antihypertensive effects by reducing aldehyde conjugate/AGE formation and oxidative stress by improving insulin-resistance and endothelial function, or by normalising calcium channels and peripheral vascular resistance.

Asplund[22] concluded that there was no evidence of an association between blood pressure (BP) and intakes of either carotene or Vitamin E. A study by Chen *et al*[23] reported significant associations between hypertension and serum levels of Vitamins A and E and β-carotene, after controlling for factors like age, sex, ethnicity, education, body mass index, alcohol consumption, history of diabetes, dietary intakes of sodium, potassium, saturated fat and total energy intake. β-carotene, uric acid, MDA and homocysteine were significantly associated with hypertensive status.

Two intervention studies have examined the effect of β-carotene, in combination with Vitamins C and E, in the treatment of hypertension, with a beneficial effect on systolic BP in one, but no effect in the other. The effect of β-carotene on BP warrants further studies. Uric acid is widely distributed in the body in relatively high concentrations and is an efficient scavenger of hydroxyl radicals, superoxides and singlet oxygen species, and can chelate transition metals. It contributes up to 60% of the total antioxidant capacity (TAC) in healthy subjects. Uric acid levels are frequently elevated in hypertensive patients. While uric acid is protective because of its antioxidant properties, it may also be harmful as it may

have a pathogenic role in hypertension and cardiovascular disease. In animal models, uric acid has been demonstrated to stimulate afferent arteriolopathy and tuberointerstitial disease, leading to hypertension. It also causes endothelial dysfunction, vascular smooth muscle proliferation, and impaired nitric oxide production[24], thereby contributing to cardiovascular and renal vascular disease. Given this complexity of relationship of uric acid and hypertension, the overall effect of slightly raised uric acid levels in hypertensive subjects is difficult to decide.

Malondialdehyde is a reliable marker of lipid peroxidation and perioxidative tissue injury[25]. It has been shown to be elevated in animal models of experimentally induced hypertension, suggesting that it is a consequence rather than a cause of hypertension. This suggests that active lipid peroxidation is occurring in essential hypertension, and this may be related to the development of atherosclerosis.

In a study by Parslow *et al*[26], decreased plasma level of β-carotene and elevated level of uric acid was associated with hypertension. Hypertension was also associated with higher levels of malondialdehyde. The study by Parslow *et al* found no significant association between plasma levels of Vitamins A and E and hypertension status in comparison to the findings reported by Chen *et al*, in which these measures were strongly associated with hypertension. The hypertensive state is frequently associated with elevation of uric acid, as reported by Parslow *et al*. Hypertension is associated with decrease in renal blood flow, which leads to greater reabsorption of urate. Another mechanism of increased urate may be through microvascular disease and local tissue ischaemia produced by hypertension. The study by Parslow *et al* showed that hypertension was associated with lower levels of plasma β-carotene and higher levels of uric acid but not with levels of plasma Vitamins A and E or total antioxidant capacity.

These findings are consistent with previous reports of increased oxidative stress in hypertension, but the direction of causality cannot be deduced from this study. Whether it is cause or consequence, reducing oxidative stress is likely to be beneficial. Longitudinal studies are necessary to decide causality. The benefits of antioxidants in hypertension should be examined in well-designed studies.

In a study by Bello Klein *et al*[27], rats were made hypertensive by the administration of the nitric oxide synthase inhibitor nitro-L-arginine (LNA). Hearts from these animals were analysed for lipid peroxidation (LPO), ψ-glutamylcysteine-synthetase (ψ-GCS), glutathione disulfide reductase (GR), glutathione peroxidase (GSHPx), catalase (CAT), superoxide dismutase (SOD), and total radical trapping potential (TRAP) activities. LNA treatment significantly increased the mean arterial blood pressure, heart rate, LPO and SOD activity. Significant reduction was found in levels of ψ-GCS, GR, nonselenium GSHPx, catalase and TRAP. These data suggest that LNA-induced hypertension is associated with increased myocardial oxidative stress.

A study was conducted by Niu Tian *et al*[28] to test the hypothesis that oxidative stress in Dahl salt-sensitive (SS) rats on a high-sodium intake contributes to the progression of renal damage, decrease in renal haemodynamics, and development of hypertension. It was studied whether antioxidant therapy using vitamins C and E could help prevent renal damage and reductions in GFR and renal plasma flow and attenuate the increase in blood pressure in salt-sensitive rats. The study showed that in rats with high-sodium diet, vitamin C and E treatment significantly decreased renal cortical and medullary O_2^- release, mean arterial pressure, urinary protein excretion, glomerular necrosis, and renal tubulointerstitial damage. GFR and renal plasma flow significantly increased in the high-sodium plus vitamins C and E group compared with the high-sodium diet group alone. This suggests that increases in reactive oxygen species are associated with decreases in renal haemodynamics in salt-sensitive hypertension. For many years, it has been believed that renal damage in hypertension is directly caused by exposure of the kidney to high pressure. However, in the study by Niu Tian *et al*, data indicate that the improvement in renal dysfunction in the high-sodium plus vitamin group could have been caused by either a decrease in arterial pressure or a reduction in free radicals in the kidney, or a combination of the two effects. The decrease in arterial pressure in rats on high-sodium and vitamins intake was ~ 20 mm Hg compared with the high-sodium rats. Thus, the mean arterial pressure of the vitamin-treated rats remained elevated at 160 mm Hg. However, the renal cortical and

medullary O_2^- release significantly decreased in the high-sodium plus vitamins C and E group. Because the decrease in arterial pressure was only moderate in the rats treated with vitamins and high-sodium diet, it is possible that the reduction in O_2^- release played an important role in the improvement in renal dysfunction and damage. As recommended by the American Institute of Nutrition, the daily amount of vitamin E in humans is 30 IU/d or 0.43 IU/kg per day. In a study in hypercholesterolaemic patients by Roberts *et al*[29], a significant decrease in plasma isoprostane was seen only when vitamin E intake was increased 25- to 100-fold over the recommended daily amount. Several clinical trials have been performed to determine if vitamin treatment can improve cardiovascular disease. Although variable results have been found, some studies have shown that treatment of hypertensive patients with vitamin C lowers blood pressure[30]. Most clinical studies on vitamin E used doses 400 IU/d, and no reduction in cardiovascular risk has been noted; however, when 800 IU/d of vitamin E was used[31,32], significant decrease in cardiovascular risk occurred. A second reason why vitamin E was ineffective in some clinical studies is that vitamin E can become a free radical in the body, but vitamin C can convert the pro-oxidant vitamin E radical back to vitamin E.

In a study by Martin Rodriguez-Porcel *et al*[33], pigs were studied after 12 weeks of renovascular hypertension without or with daily supplementation of antioxidants (100 IU/kg vitamin E and 1 g vitamin C), and compared with normal controls. Myocardial perfusion and microvascular permeability were measured by electron beam computed tomography before and after two cardiac challenges (intravenous adenosine and dobutamine). The regimen of vitamin C and E preserved endogenous scavenger enzyme activity, decreasing the abundance of superoxide anion. The impaired myocardial perfusion response to adenosine observed in hypertensives was preserved in rats who received antioxidants. Antioxidant intervention had little effect on the hypertension-induced myocardial vascular dysfunction observed in response to dobutamine. The greater improvement in the responses to adenosine than to dobutamine challenge in vitamin-treated HT might at least in part be related to their different mechanisms of action. This study demonstrates that the impaired myocardial perfusion and permeability in early hypertension are significantly improved by long-term antioxidant intervention. These results support the involvement of oxidative stress in myocardial vascular dysfunction in hypertension.

Tubulointerstitial infiltration of lymphocytes and macrophages is associated with the generation of reactive oxygen species (ROS) in experimental models of hypertension. A study by Bernardo Rodriguez-Iturbe *et al*[34] demonstrated that an antioxidant-enriched diet that included vitamin E, vitamin C, selenium, and zinc reduces the renal interstitial inflammation, decreases renal tissue content of malondialdehyde and improves hypertension. Reactive oxygen species have been shown to activate nuclear factor-B, which can in turn promote transcription of genes encoding proinflammatory cytokines. This phenomenon can potentially explain the prevention of the inflammatory infiltration of the kidney in the antioxidant-treated group. These findings point to interrelation between oxidative stress and inflammatory reactivity in the pathogenesis of hypertension. The presence of oxidative stress and its role in elevation of arterial pressure has been shown in various other forms of hypertension including that seen with lead exposure[35], chronic renal insufficiency[36], salt sensitivity[37], angiotensin infusion[38], pre-eclampsia[39], renal artery stenosis[40], and coarctation of the aorta[41]. Earlier studies have documented the beneficial effects of vitamin E and vitamin C in ameliorating hypertension in hypertensive animals and improving endothelial function in hypertensive humans. In addition, selenium (the critical constituent of the antioxidant enzyme glutathione peroxidase) has been shown to retard progression of renal disease in diabetic and nondiabetic animals. Finally, zinc is an important component of cytoplasmic (Cu-Zn SOD) and extracellular superoxide dismutase, which serves as the frontline of defense against reactive oxygen species. Zinc deficiency has been shown to aggravate hypertension. This explains how amelioration of oxidative stress with antioxidant therapy improves hypertension.

A study was done by Czernichow *et al*[42], to assess the effects of supplementation of a combination of antioxidant vitamins and trace elements, upon the 6.5-year risk of developing hypertension. Despite an inverse association between baseline plasma levels of β-carotene

in men and the risk of developing hypertension, this study did not demonstrate any beneficial effect of low-dose antioxidant supplementation upon the risk of developing hypertension.

A study was performed by Subhash *et al*[43] in south Indian population to investigate the total antioxidant status (TAS) and the extent of oxidative DNA damage in lymphocytes and their relation with essential hypertension. DNA damage was significantly increased in hypertensive patients as compared with the control group. There was a significant decrease in plasma TAS value in essential hypertensive groups as compared to normotensive controls. The major increase in lymphocyte DNA damage was observed in newly diagnosed hypertensive patients compared with hypertensive patients who were already on drug therapy. Decreased TAS levels, which reflect increased oxidative stress, may be the reason of increased total lymphocyte DNA damage in this study.

A study done by de la Sierra *et al*[44] to assess the correlation between endothelial dysfunction and the serum levels of biomarkers of oxidative stress in essential hypertension showed reduced serum levels of selenium, vitamin C, erythrocyte glutathione peroxidase in patients compared to controls. In this study, treatment-naive essential hypertensives showed a relationship between the endothelial dysfunction on one hand and serum markers of inflammation, remodelling, and antioxidants on the other.

The mechanism underlying blood pressure reduction in the high fruits and vegetables arm of the Dietary Approaches to Stop Hypertension (DASH) study is unknown but may include potassium, magnesium and fibre. A study was done by Al-Solaiman *et al*[45] to study the effects of minerals and fibre separately from other components of DASH on BP in individuals with metabolic syndrome and pre-hypertension to stage 1 hypertension (obese hypertensives). This study showed that DASH is more effective than potassium, magnesium and fibre supplements for lowering BP in obese hypertensives, which suggests that high intake of fruits and vegetables in DASH lowers BP and improves endothelial function by nutritional factors in addition to potassium, magnesium, and fibre. Salt induces oxidative stress in salt-sensitive animals and human beings. It is not clear whether in salt-sensitive subjects the Low-Sodium Dietary Approaches to Stop Hypertension (LS-DASH) reduce oxidative stress more than DASH. A study was done by Al Solaiman *et al*[46] to assess the effects of DASH and LS-DASH on oxidative stress. This study showed that in salt-sensitive but not salt-resistant subjects, LS-DASH is associated with lower values of systolic blood pressure, urine F2-isoprostanes (a marker of oxidative stress) and aortic augmentation index (a measure of vascular stiffness). The results suggest that LS-DASH decreases oxidative stress, improves vascular function and lowers blood pressure in salt-sensitive but not salt-resistant volunteers.

Conclusion

Oxidative stress plays an important role in the pathogenesis of hypertension. A number of sources of reactive oxygen species have been identified like NADPH oxidase, endothelial NO synthase, and xanthine oxidase. Targeted overexpression of antioxidant systems and interference with expression of oxidant systems has been successfully used in animal models of hypertension. It is expected that these strategies will eventually be translated to human disease. At present, nontoxic measures like antioxidant vitamins are the only available treatments for oxidative stress in humans.

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POST-GRADUATE CLINIC

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Juvenile Systemic Sclerosis

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Abstract

Systemic sclerosis (SSc) is a multisystem disorder characterised by fibrosis affecting the dermis (scleroderma) and vasculature of the lungs, kidneys, CNS, heart and gastrointestinal tract. Juvenile systemic sclerosis (JSSc) is a rare disease. We encountered a 13-year-old female child and hereby present the clinical, biochemical, serological, radiological features and follow-up of this child with a review of literature.

Key words: Systemic sclerosis, Juvenile, Scleroderma

Case

A 13-year-old female child started having pain in both lower limbs with tightening of skin and restriction of movements of the feet 1½ years back. Over a period of six months, this tightening of skin and pain in joints involved the upper limbs and face resulting in restriction of joint movements and mouth opening. There was no history of joint swelling. There were no aggravating and relieving factors. Simultaneously, the patient experienced episodes of bluish discolouration of finger tips on exposure to cold (Raynaud's phenomenon). One month back she had sudden appearance of dark brown rashes over the face, trunk, and upper limbs which were non-pruritic and non-progressive. Ten days back she had watery loose stools, up to 10 times per day, with no blood but accompanied with colicky pain in the abdomen which lasted for 5 days. Since last 7 days she started complaining of difficulty in swallowing both solids as well as liquids. For the same duration she had cough with expectoration of whitish sputum without blood. There was no history of fever, epigastric or chest pain, dyspnoea on exertion, or passage of dark-coloured urine. There was no history of constipation. Family, personal, and past histories were noncontributory.

Clinical examination revealed a thin built markedly pale child with sparse hair and prominent bony markings. Pitting pedal oedema was present. Heart rate was 132 beats/min, respiratory rate was 20/min, regular, andblood pressure was 100/60 mmHg. There was no significant lymphadenopathy. Her face was mask-like with thin lips, complete loss of facial lines and beaking of nose. The skin over her face was tense and taut and could not be pinched (Fig. 1). Mouth opening was restricted (2 cm) (Fig. 2). Skin over the extremities was atrophic, adherent to the underlying structures and could not be pinched. There were multiples well-defined, discrete-to-confluent, pin head to 1 cm sized, hyperpigmented, non-scaling, non-blanching and non-erythematous macules over face, hands, trunk and back. Musculoskeletal system examination revealed generalised wasting of muscles and bilateral flexion deformity of hip, ankle, knee, wrist and all distal and proximal interphalangeal joints (Fig. 3). There was restriction of movement at all these joints without swelling. There was cheesy material oozing out from both olecranons (calcinosis cutis) (Fig. 4). Cardiovascular system examination revealed a gallop rythym, a short ejection

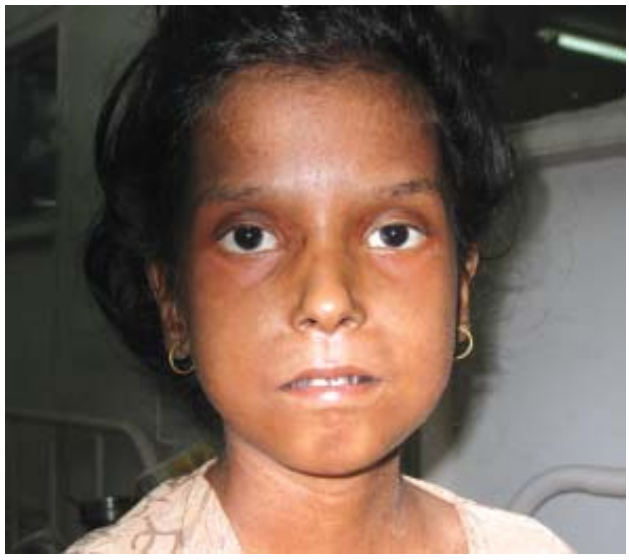

Fig. 1: *Face showing loss of folds, lines, taut skin, pinched nose.*

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systolic murmur in parasternal area of 3rd and 4th left intercostal space. The CNS and respiratory system examinations were normal. Nail fold capillaroscopy with ophthalmoscope (40D) showed tortuous dilated capillaries with dropouts.

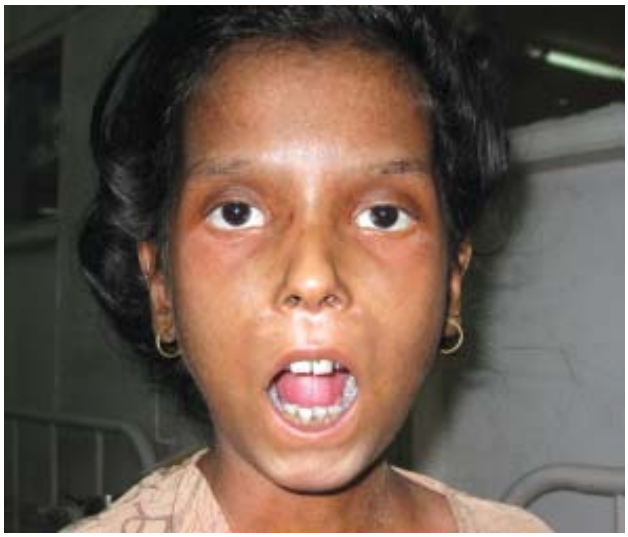

Fig. 2: *Decreased mouth opening.*

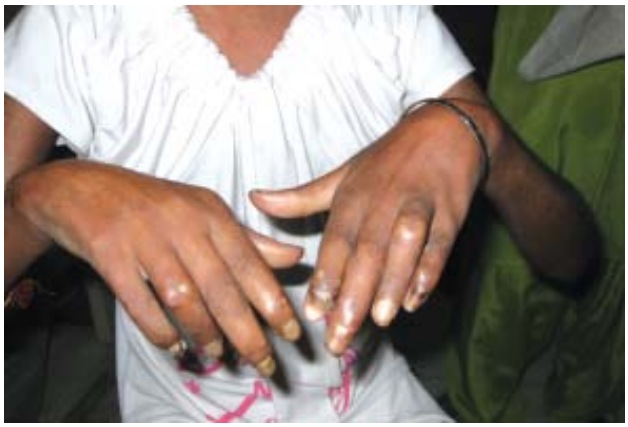

Fig. 3: *Sclerodactyly, flexion contractures of IP joints.*

Investigations revealed severe anaemia (Hb 6.9 g/dl) with corrected reticulocyte count of 5.5%, positive direct Coomb's test (2+) and thrombocytopenia (0.36 lakhs/ mm^3). TLC was 5,900/mm^3, polymorphs 55%, lymphocytes 45%, MCV 93.3 fl, and the peripheral smear showed a dimorphic picture with anisopoikilocytosis and tear drop cells. PT/aPTT were normal, and stool for occult blood was negative. Blood sugar, serum electrolytes, calcium, phosphorus, renal function tests and lipid profile were normal. LFT showed slightly raised enzymes (SGOT 84 units and SGPT 67 units) with normal serum bilirubin, total protein of 6.4 mg/dl and albumin 2.6 mg/dl. Serum iron studies revealed iron 34 mg/dl and saturation of 4.6%. LDH was slightly raised and CPK was raised 848 units (normal upto 200). C-reactive protein and rheumatoid factor were positive and ESR was 120 mm/h. Urine examination showed microalbuminuria 94 mg/dl (normal < 30), microscopic examination was normal and culture was sterile.

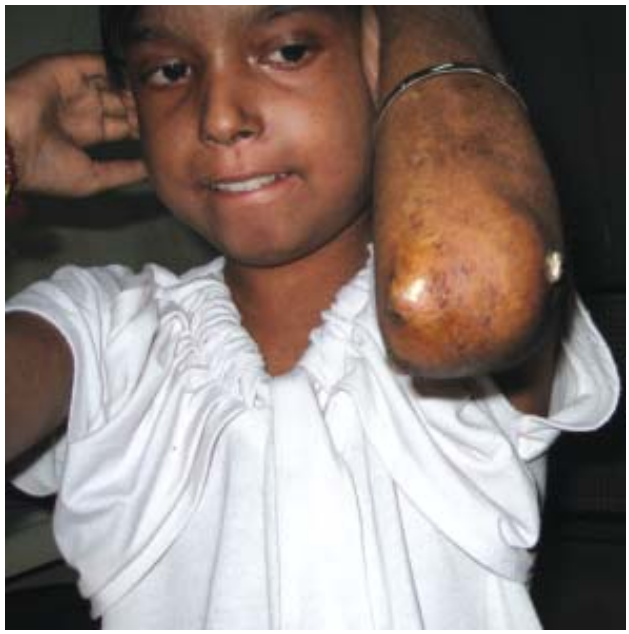

Fig. 4: *Calcinosis cutis over elbow.*

There was cardiomegaly in chest X-ray, ECG was normal. Echocardiography showed all chambers and valves to be normal with mild pericardial effusion and EF of 65%. USG abdomen revealed coarse echotexture of liver with mild ascites. Barium swallow showed dilated oesophagus in mid- and lower third with no filling defect, but gastro-oesophageal reflux was present. Barium meal follow-through revealed dilated small bowel loops with diffusely increased mucosal folds (classic "hide-bound" sign seen in scleroderma). High-resolution CT chest was normal. Pulmonary function test could not be performed at this time due to restricted mouth opening. Skin biopsy revealed hyperkeratotic follicular plugging and thinned-out epidermis. Papillary dermis was unremarkable. Reticular dermis and subepidermal tissue was partially replaced by thick collagen bundles. Sweat glands were upto the level of mid-dermis. There were no significant

inflammatory infiltrate. Features were consistent with systemic sclerosis.

Serology revealed negative ANA (done by immunoflourescence on Hep2 cell) and raised U1 RNP antibodies (uridine ribonucleoprotein) of 28.27 units/ml (normal < 5.0), anti scl-70 antibodies of 99.60 units/ml (normal < 30), and anticentromere IgG antibodies of 39.41 units/ml (normal < 3). Anti-Ro and anti-La antibodies were negative. Immunoglobulin levels and C3, C4 were normal. Anti-erythrocyte antibodies, both warm and cold, antiplatelet antibodies and Donath Landsteiner antibodies could not be done due to financial constraints.

Based on the history, examination and investigations, the child was finally diagnosed as juvenile diffuse systemic sclerosis with immune haemolytic anaemia and thrombocytopenia. She was managed with pulse methyl prednisolone therapy for 3 days along with diuretics followed by oral prednisolone, inj. methotrexate, tab nifedipine, tab d-penicillamine, tab folic acid, iron, and physiotherapy. Two weeks later, her Hb had increased to 8.4 g% and platelets to 1.6 lakhs/mm^3 with disappearance of pedal oedema and regression of heart size. Steroids were gradually tapered and stopped over a period of 3 months.

On follow-up after 3 months, she is mobile and walking, with no anaemia, no fever, no dysphagia and her mouth opening has increased to 4 cm. However, the whole skin is atrophied and wasted and the face is expressionless. Raynaud's phenomenon, calcinosis cutis, some flexion deformity of both wrists, knees, and all proximal and distal interphalangeal joints are still present. Indirect and direct Coomb's tests are negative. Hb is 12 g%, retic count is 1%, CRP is positive and LFTs are normal. PFT which was now possible, revealed moderately restrictive lung disease.

What is the epidemiology of juvenile systemic sclerosis (JSSc)?

JSSc is a rare form of systemic sclerosis. Few case series report that less than 10% of SSc cases have their onset before the age of 20 and fewer than 2% before the age of 10[1]. Youngest reported case is 6 months old[2]. Female preponderance has been found to be 7:1[3].

How is the diagnosis of juvenile systemic sclerosis made?

The adhoc committee on classification criteria for juvenile systemic sclerosis – a combined effort of the paediatric Rheumatology European Society, the American College of Rheumatology, and the European League Against Rheumatism – have developed the new classification criteria for JSS as given below[4]. Evidence of proximal cutaneous sclerosis and at least 2 of 20 predefined minor criteria are required for a diagnosis of juvenile systemic sclerosis (Table I).

Table I: Criteria for diagnosis of juvenile systemic sclerosis.

MAJOR CRITERION (Required)	
Proximal (to MCP/MTP joints) skin sclerosis or induration of the skin	
MINOR CRITERIA (At least two required)	
Cutaneous	Sclerodactyly
Peripheral vascular	Raynaud's phenomenon, nailfold capillary abnormalities, digital tip ulcers
Gastrointestinal	Dysphagia, gastro-oesophageal reflux
Cardiac	Arrhythmias, heart failure
Renal	Renal crisis, new-onset arterial hypertension
Respiratory	Pulmonary fibrosis (HRCT/ radiograph), decreased DLCO, pulmonary artery hypertension
Neurologic	Neuropathy, carpal tunnel syndrome
Musculoskeletal	Tendon friction rubs, arthritis, myositis
Serologic	Antinuclear antibodies, SSc selective autoantibodies (anticentromere, anti-topoisomerase I (Scl 70), anti-fibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III)

What are the common clinical manifestations of JSSc?

The common clinical manifestations of JSSc are:

1. Proximal sclerosis (100%)
2. Sclerodactyly (91%)

3. Raynaud's phenomenon (83%)
4. Nailfold capillary abnormalities (74%)
5. Digital pitting (65%)
6. Arthralgia (61%)
7. Oedema (52%)
8. Calcinosis (48%)
9. Weight loss (48%)
10. Dysphagia (39%)
11. Arthritis (35%)
12. Muscle weakness (35%)
13. Dyspnoea (26%)[3].

How is juvenile systemic sclerosis different from adult systemic sclerosis (SSc)?

For adults, one major or two of the three minor diagnostic criteria should be present for diagnosis of systemic sclerosis (Table II). The minor criteria for classification of JSSc are more numerous than those used for adults[5].

Table II: Diagnostic criteria of adult systemic sclerosis.

MAJOR
Proximal scleroderma: typical sclerodermatous skin changes (tightness, thickening, and non-pitting induration, excluding localised forms of scleroderma) involving areas proximal to the metacarpophalangeal or metatarsophalangeal joints
MINOR
Sclerodactyly: sclerodermatous skin changes limited to digits
Digital pitting scars resulting from digital ischaemia
Bi-basilar pulmonary fibrosis not attributable to primary lung disease

JSSc appears to be less severe than in adults because children have less internal organ involvement, a less specific autoantibody profile, and a better long-term outcome[6]. Children show less frequent organ involvement except for the prevalence of arthritis, the severity of raynaud's phenomenon, as shown by digital infarcts. Interstitial lung involvement signs are less frequent in children. The differences become less evident during follow-up. For other internal organs, involvement is similar except for gastro-oesophageal dysmotility, arterial hypertension, and musculoskeletal symptoms, all of which are more common in adult SSc except for muscle inflammation which is distinguishingly more in JSSc[7]. Also, there is late development of pitting scars or pulmonary fibrosis in radiographs in children with JSSc. Hence, the diagnostic citeria for adult patients with systemic sclerosis are different from JSSc[8].

Which organ systems are involved in JSSc?

The various organ systems involved in JSSc are skin, GIT, respiratory, renal, musculoskeketal and cardiovascular. The pattern of organ involvement is the same in JSSc and adult SSc patient[7,8,9,12].

Skin: Raynaud's phenomenon is often the earliest manifestation of scleroderma and may precede extensive skin and internal organ involvement by years[8]. The typical sequence of colour change is blanching and cyanosis, followed by hyperaemia. Presence of two of the three stages is sufficient for identification. It results from arterial spasm on exposure to cold.

Systemic sclerosis may have a preliminary oedematous phase characterised by puffiness around fingers, on dorsum of hands or face lasting several months before chronic fibrosis develops. Decrease in oedema is associated with tightening of skin which spreads proximally from the hands. Loss of subcutaneous tissue in the face can result in a small oral stoma with restriction of mouth opening (Fig. 2). Skin ulceration over pressure points may be associated with subcutaneous calcifications (Fig. 4). Later, atrophic skin can become shiny and waxy in appearance. Loss of tissue at the fingertips may be associated with ulceration. Distal phalanges may exhibit resorption of the distal tufts (acro-osteolysis). The fingers assume a tapered appearance associated with tightened skin (sclerodactyly); and later, secondary flexion contractures develop with limitation of motion (Fig. 3). As lesions spread proximally, flexion contractures in elbows, hips and knees may be associated with secondary muscle weakness and atrophy. Other chronic changes include epidermal thinning, hair loss, and decreased sweating. Hyperpigmented post-inflammatory changes surrounded by atrophic depigmentation may give a salt-and-pepper appearance to some skin lesions.

Pulmonary disease includes arterial and interstitial involvement, occurs in around 41 - 53% of patients and

varies from minimal disease to a progressive course with decreased exercise tolerance, dyspnoea at rest, and right-sided heart failure. Chest roentgenograms may appear normal in the early course. Pulmonary function tests may be abnormal even in the presence of normal chest X-ray. Evidence of early involvement of pulmonary interstitial disease is by performing pulmonary function tests, including evaluation of oxygen diffusion by diffusion of carbon monoxide capacity (DLCO) and high-resolution CT (HRCT).

Renal arterial disease can cause chronic or severe episodic hypertension. It is involved in about 10 - 14% of patients.

Gastrointestinal (GI) involvement is most commonly manifested by dysphagia due to oesophageal dilatation caused by fibrosis. Dilated intestinal loops can result in malabsorption, diarrhoea and failure to thrive. GI system is found to be affected in 58 - 88% of patients.

Cardiac fibrosis has been associated with arrhythmias, pericarditis, ventricular hypertrophy, right-sided heart failure and decreased cardiac function. It is involved in 25 - 40% of patients of JSS.

The evaluation of patients with JSS should include pulmonary function tests, HRCT chest, diffusion studies of lung, contrast studies of the upper gastrointestinal tract to evaluate oesophageal motility, and echocardiography to identify pulmonary arterial hypertension.

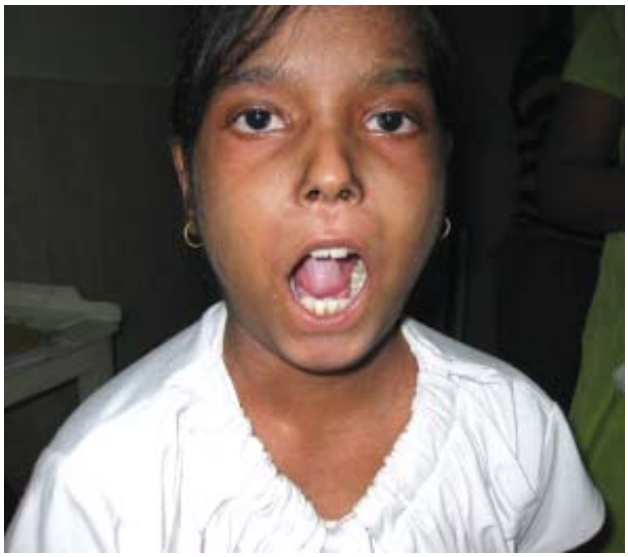

Fig. 5: *Mouth opening increased with threapy.*

What is the prognosis of a patient with JSSc?

In a multinational survey, of the 135 children with JSSc, 82 had inactive disease on medication, 16 were in remission, and 8 had died on 5-year follow-up. 90% were fully active in daily life. The causes of death were heart failure, renal failure, and sepsis. The 1-year survival rate was 99%, the 2-year rate was 97% and the 4-year survival was 95%. There was a favourable outcome in most patients with childhood onset JSSc and a significantly better survival than in the adult SSc patients[3]. The factors responsible for poor outcome were higher frequency of organ involvement at the time of diagnosis – particularly cardiac, respiratory and gastrointestinal system. Significant predictors of morbidity were fibrosis on chest X-ray, pericarditis, and raised serum creatinine levels[10].

How is immune haemolytic anaemia and thrombocytopenia managed in this patient?

Haemolytic anaemia is rare in SSc with only 20 cases reported in literature so far, all of whom are adult SSc patients[11]. Immune haemolytic anaemia and thrombocytopenia respond well to pulse methylprednisolone (30 mg/kg/d) and then maintenance oral steroids are given at 1 - 2 mg/kg/d – till the time Hb is normal and direct comb's test negative – and then tapered.

What are the treatment options available for JSSc?

Immunosuppressive agents like methotrexate (0.5 - 1 mg/m^2 SC once a week) used in the early stages of the disease may help curb inflammation. Corticosteroids (oral prednisolone 2 mg/kg OD after breakfast) also help in the early stages but may exacerbate hypertension later in the course of the disease. D-Penicillamine – an anti-fibrotic agent – was used frequently earlier. Due to an adverse safety profile, its use has decreased. Arthritis needs treatment with NSAIDs along with physical and occupational therapy to improve flexion contractures and maintain muscle strength, and spring-loaded splints in selected patients. Angiotensin-converting enzyme (ACE) inhibitors and receptor antagonists are used for treatment of renal hypertension. Prostacyclin analogues like Iloprost,

treprostinil, epoprostenol are used for treatment for pulmonary arterial hypertension.

If Raynaud's phenomenon persists despite local measures (keeping hands warm during cold exposure with gloves), therapy with calcium channel blockers (sustained release nifedipine, amlodipine besylate), angiotensin-converting enzyme inhibitors (captopril, enalapril), and topical vasodilators (nitroglycerine paste) may be successful in preventing fingertip ulcerations. Vascular compromise threatening to proceed on to gangrene and autoamputation of the distal digits may respond to parenteral administration of prostaglandin E_1 (alprostadil)[12].

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POST-GRADUATE CLINIC

JIACM 2011; 12(2):134-40

Portal Vein Thrombosis – Clinical Profile

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Abstract

Portal vein thrombosis is commonly forgotten as a possible cause of abdominal pain, portal systemic encephalopathy, or gastrointestinal haemorrhage caused by oesophageal varices, splenomegaly, and/or ascites. It can complicate the underlying pathology and can increase morbidity and mortality. There can be varied aetiology and pathogenesis of portal vein thrombosis. Usually, the radiologic diagnosis is made either by duplex Doppler ultrasonography and/or colour Doppler ultrasonography. CT scan, magnetic resonance angiography (MRA) and arterial portography or splenoportography. MRI seems a very promising method. The treatment, course, and the prognosis of portal vein thrombosis depends on the aetiology of the disease. Here we are presenting three cases of portal vein thrombosis with different aetiology.

Key word: Portal vein thrombosis.

Case 1

A 40-year-old lady presented with history of pain in abdomen lasting for 15 days. She felt pain mainly in the upper abdomen. Pain was dragging in nature, no radiation to any side. There was no associated nausea, vomiting, jaundice, fever, or GI bleed. There was no history of significant past medical illness, alcoholism or significant family history.

General physical examination revealed only mild icterus. On systemic examination, she has mild hepatomegaly (3 cm), non tender, firm, smooth surface and splenomegaly (6 cm). Gynaecological examination was normal.

Her routine laboratory investigations were normal except hyperbilirubinaemia (serum bilirubin: total 2.1 mg/dl, direct 1.2 mg/dl). Liver enzymes, serum proteins, and prothrombin time were normal. Viral markers were nonreactive. ANF, CRP negative, chest X-ray normal. USG abdomen showed enlarged liver with coarse echoexture and a hyperechoic lesion in the right lobe of liver with splenomegaly. The portal vein was 13.5 mm with hypoechogenicity in the lumen (? thrombus). USG colour Doppler confirmed portal vein thrombosis. Upper GI endoscopy revealed grade I oesophageal varices. Thrombophilia profile and cancer markers were within normal range. The patient was treated with inj. enoxaparine 1 mg/kg bid. Her symptoms improved and she was discharged for OPD follow-up.

However, she was readmitted after 1 month with ascites. Fluid was transudative, and cell counts were normal. CECT abdomen showed an enlarged liver with surface nodularity, and an irregularly enhancing inhomogenous lesion of size 7.8 x 6.8 cm in the right lobe of liver (mass lesion with malignant transformation) with portal vein thrombosis with collateral formation with splenomegaly and ascites. USG guided FNAC of liver mass was suggestive of adenocarcinoma. A final diagnosis of liver cirrhosis with adenocarcinoma of liver with portal vein thrombosis with portal hypertension was made. She was put on supportive therapy as she could not afford further

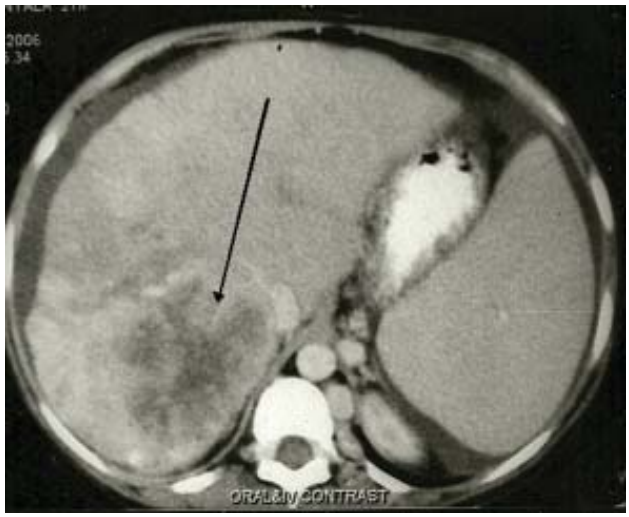

Fig. 1: *CT showing hepatocellular carcinoma (arrow).*

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treatment. A repeat CT abdomen showed multifocal hepatocellular carcinoma (Fig. 1) with portal vein thrombosis (Fig. 2) in a cirrhotic liver. She died after 4 months.

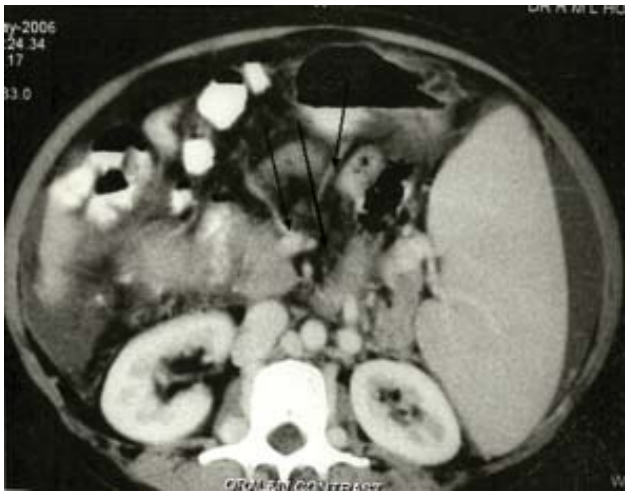

Fig. 2: *CT abdomen demonstrates thrombus as a low attenuation structure in the portal vein with collateral formation (arrow heads) in a patient with hepatocellular carcinoma.*

Case 2

A 19-year-old lady who had acute pancreatitis 3 months back presented with mild pain in upper abdomen for 1 month with increased intensity of pain for 1 day associated with fever. The pain was not colicky, radiating to the back. On clinical examination, she had pallor and generalised tenderness over the abdomen (mainly over left hypochondrium) with evidence of free fluid.

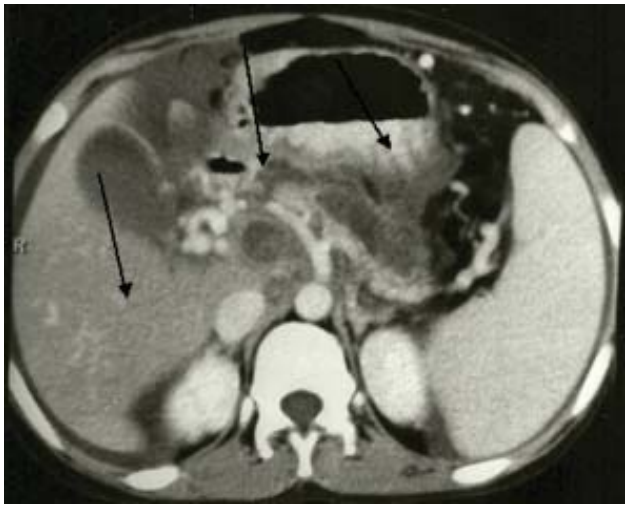

Fig. 3: *CECT abdomen showing necrotising pancreatitis with portal vein thrombosis and ascites (arrow).*

All of her routine investigations were normal except for mild anaemia and very high levels of serum lipase and amylase. Ascitic fluid analysis was exudative with lymphocytic predominance. On USG abdomen, features of acute pancreatitis were present along with ascites, and an echogenic thrombus in the portal vein. USG colour Doppler confirmed portal vein thrombosis with collaterals. Her CECT abdomen also confirmed the diagnosis of acute pancreatitis with ascites and portal vein thrombosis (Fig. 3). UGI endoscopy was normal.

The patient was managed conservatively with anticoagulants and other supportive measures, and she improved. Repeat USG colour Doppler 2 months later showed resolution of the thrombus. Anticoagulation therapy was then discontinued.

Case 3

A 62-year-old lady presented with haematemesis and malena for 2 days. She had co-morbidities of diabetes mellitus and hypertension since the last 8 years. She was receiving ATT since last 2 months for pulmonary TB. There was a similar history of upper GI bleed one month ago which was managed conservatively. Investigations done a month ago revealed liver cirrhosis with portal hypertension with cholelithiasis. On upper GI endoscopy, she had grade II-III oesophageal varices. Her routine investigation revealed anaemia. Threr was no past h/o alcohol abuse. Viral markers were negative.

She underwent endoscopic variceal ligation and other supportive care, and subsequently discharged. She had 2 more episodes of upper GI bleed, which were managed conservatively.

On examination, there was mild pallor, decreased breath sounds in the left mammary and infrascapular region. There were no signs of hepatic cell failure.

On routine laboratory investigations, there was anaemia and leucopenia. Platelet counts were marginally low (1,29,000). Blood sugar was elevated, but the patient was not in ketosis. USG abdomen this time revealed an echogenic thrombus in a dilated portal vein with liver cirrhosis and splenomegaly. Colour Doppler USG and

CECT abdomen (Fig. 4) confirmed the presence of thrombus. Thrombophilia profile was normal.

Thus a diagnosis of type 2 DM with hypertension with pulmonary TB with liver cirrhosis with oesophageal varices with portal vein thrombosis was made.

Patient refused to undergo any further endoscopic procedure; therefore, was managed conservatively.

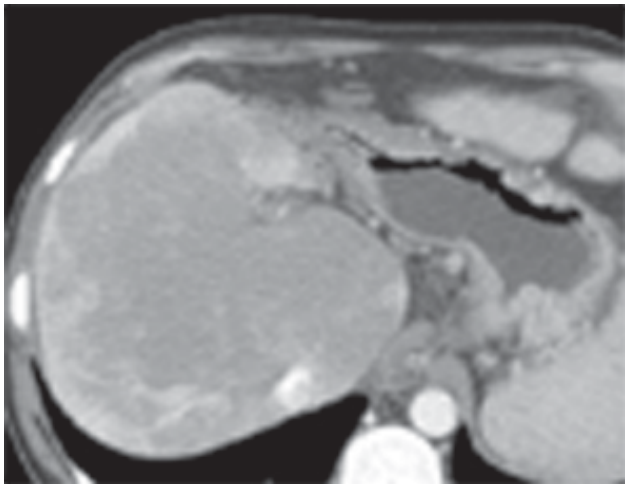

Fig. 4: *CECT abdomen showing cirrhosis of liver with portal vein thrombosis (arrow).*

How does a patient of PVT present?

PVT is commonly forgotten as a possible cause of abdominal pain. It can present acutely with sudden onset of right upper quadrant pain, nausea and/or fever. In most patients, PVT occurs slowly and silently with patients presenting with vague abdominal pain, fever, portal systemic encephalopathy or gastrointestinal haemorrhage caused by oesophageal varices, splenomegaly, and/or ascites[1].

The signs and symptoms of PVT can be subtle or nonspecific, and they can be overshadowed by those of the underlying illness. PVT is often not discovered until gastrointestinal haemorrhage develops, or unless the thrombosis is discovered during routine surveillance for a known underlying pathologic condition[1].

Splenomegaly is found in 75 - 100% of patients, most presenting in the chronic stage. Mild hepatomegaly is often present, as is right upper quadrant epigastric tenderness, especially in the acute setting. Ascites is found infrequently. Stigmata of chronic liver disease, such as spider angiomata or palmar erythema, are usually found in the presence of underlying liver disease.

Abnormalities of the extrahepatic biliary tree may occur in 80% of cases due to compression by choledochal or periportal varices or from ischaemic stricturing. These findings manifest by jaundice, cholangitis, haemobilia, cholecystitis, or a hilar mass that can be mistaken for a cholangiocarcinoma.

Portal vein thrombosis (PVT) is being recognised with increasing frequency with the use of ultrasonography. Transient PVT is also being recognised with increasing frequency, partly because of the great increase in the use of ultrasonography in the evaluation of patients with abdominal inflammation such as appendicitis. Hypercoagulable syndromes can lead to portomesenteric and splenic vein thrombosis. Patients with these conditions may present with acute or subacute intestinal angina. In late stages, patients may have variceal bleeding[2,3,4].

All three of our patients presented with symptoms of underlying illness. The cases presented show that patients with PVT can present to the internist, gastroenterologist and surgeons.

What is the pathophysiology of PVT?

The portal vein forms at the junction of the splenic vein and the superior mesenteric vein behind the pancreatic head, and it can become thrombosed or obstructed at any point along its course. In cirrhosis and hepatic malignancies, the thromboses usually begin intrahepatically and spread to the extrahepatic portal vein. In most other aetiologies, the thromboses usually start at the site of origin of the portal vein. Occasionally, thrombosis of the splenic vein propagates to the portal vein, most often resulting from an adjacent inflammatory process such as chronic pancreatitis.

Inherited and acquired disorders of the coagulation pathway are frequent causes of portal vein thrombosis. Inherited disorders include mutations in the prothrombin gene G20210A as well as deficiencies of various intrinsic anticoagulation factors, such as protein C and protein S,

and activated protein C resistance. Acquired disorders include antithrombin III deficiency resulting from malnutrition, sepsis, disseminated intravascular coagulation, inflammatory bowel disease, liver disease, or oestrogen use.

Stasis can be another major category for portal vein thrombosis. The global resistance to hepatic blood flow produced by cirrhosis is a common cause. Sclerotherapy for oesophageal varices has been postulated as a possible mechanism though not proven thus far. The portal vein or its tributaries can be obstructed by adjacent tumour compression or invasion. Infectious and inflammatory processes may also lead to venous thrombosis. The main pathogenesis of portal vein thrombosis in pancreatitis or cholangitis/cholecystitis are suggested to be venous compression by pseudocyst and an imbalance between the blood coagulation and fibrinolysis and inflammation[5].

Formation of collaterals occurs rather rapidly as well, and they have been described as early as 12 days after acute thrombosis, though the average time to formation is approximately 5 weeks. The development of a collateral circulation, with its risk of variceal haemorrhage, is responsible for most of the complications and is the most common manifestation of portal vein obstruction. Other sequelae of the subsequent portal hypertension, such as ascites, are less frequent. Rarely, the thrombosis extends from the portal vein to the mesenteric arcades, leading to bowel ischaemia and infarction.

What are the causes of PVT?

- Idiopathic causes
- Causes secondary to tumour
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Pancreatic carcinoma
- Gastric carcinoma
- Trauma
- Iatrogenic umbilical vein catheterisation
- Abdominal sepsis
- Pancreatitis
- Perinatal omphalitis
- Appendicitis
- Diverticulitis
- Ascending cholangitis
- Myeloproliferative disorders
- Clotting disorders (hypercoagulable syndromes)
- Oestrogen therapy
- Severe dehydration
- Cirrhosis, especially in the young
- Portal hypertension

Reduced portal blood flow caused by hepatic parenchymal disease and abdominal sepsis are the major causes. In adults, cirrhosis is the major aetiology, accounting for 24 - 32% of cases of portal vein thrombosis. Neoplasms are another major cause, accounting for 21 - 24% of cases of portal vein obstruction, with hepatocellular carcinoma and pancreatic carcinoma causing most of these cases. Although less common than in children, infections (predominantly intra-abdominal) still play an important role, with a particular association to *Bacteroides fragilis* bacteraemia. Myeloproliferative disorders and inherited or acquired coagulation disorders account for 10 - 12% of cases in adults. Approximately 8 - 15% of cases have been reported to be idiopathic in the recent literature.

Our first patient had cirrhosis of liver with hepatocellular carcinoma and second patient had pancreatitis as the predisposing cause of PVT.

What is the frequency of occurrence of PVT?

The exact frequency of PVT is not known, but segmental or global PVT occurs in as many as 30% of patients with hepatocellular carcinoma. Other studies point out that the incidence of PVT in hepatocellular carcinoma varies about 20 - 30% in small HCC (< 3 cm), up to 50 - 75% in HCC > 5 cm[6].

The incidence of PVT in patients with liver cirrhosis and portal hypertension is approximately 5% (in the USA). But the incidence is up to 18% for patients referred to liver transplant units.

Extra-hepatic portal vein thrombosis is estimated to be responsible for 5 - 10% of all cases of portal hypertension. In India, extra-hepatic portal vein obstruction is reported more frequently. Of all cases of portal hypertension in developing countries, 40% are attributed to portal vein

obstruction, presumably secondary to an increased incidence of pylephlebitis (inflammation of the portal vein or any of its branches) associated with abdominal infections.

How will you confirm PVT?

Ultrasound: This is the first-line diagnostic modality because of its accuracy, affordability, and noninvasiveness.

- The thrombus is observed as an echogenic lesion within the portal vein, though a recently formed thrombus may be anechoic (i.e., not observable on standard grey-scale ultrasound).
- The addition of colour Doppler imaging is especially helpful in the detection of portal vein flow and the diagnosis of portal vein obstruction.
- The sensitivity is around 70 - 90%, with a specificity of 99%. With Doppler, the false-positive rate is 9% in patients with cirrhosis because of sluggish or turbulent portal vein flow.
- Major limitations are obesity and nonvisualisation secondary to bowel gas.
- The presence of pulsatile, arterial flow in the thrombus correlates with a malignant, not bland, thrombus.

MRI and magnetic resonance angiography (MRA): This is the next step if further portal venous information is needed. MRI is helpful if hepatic parenchymal detail is required (in hepatic malignancies), and, unlike CT scan, MRI can also quantitate portal and hepatic vessel flow, which is required in the planning of interventions, such as shunt surgery, transjugular intrahepatic portosystemic shunt (TIPS), or liver transplantation.

- Acute clot (< 5 weeks) appears hyperintense on both T1- and T2-weighted images, whereas older clots appear hyperintense only on T2-weighted images. Tumour thrombi can be differentiated from bland thrombi because they appear more hyperintense on T2-weighted images and enhance with gadolinium.
- The overall sensitivity, specificity, and accuracy of the MRA are 100%, 98%, and 99%, respectively. There is a high sensitivity for detection of submucosal, serosal, paraoesophageal collaterals.
- CT scan: Contrast-enhanced CT scan shows a thrombus as a nonenhanced intraluminal-filling defect.
- Contrast-enhanced CT scan has the advantage over ultrasound in displaying varices (sensitivity, 65 - 85%) and parenchymal hepatic abnormalities.
- The combination of CT scan and Doppler ultrasound is common in the evaluation of portal vein obstruction.

Angiography

- This examination is not usually required to confirm the diagnosis of portal vein thrombosis in the presence of CT scan or MRI.
- Angiography's major value lies in preoperative planning before shunt surgery or liver transplantation; however, it is not a prerequisite, and many transplant centres use MRI/MRA for this purpose.
- Even angiography can provide false-positive results in portal hypertension in the presence of extensive portosystemic collaterals in which mesenteric flow is directed away from a patent portal vein.

Endoscopic ultrasound (EUS): Although not a common diagnostic modality, EUS has recently been found to be 81% sensitive and 93% specific in patients with portal vein thrombosis as compared to patients with thrombus confirmed by contrast-enhanced CT scan or surgery.

Preferred examinations include duplex Doppler ultrasonography and/or colour Doppler ultrasonography, CT scan, magnetic resonance angiography (MRA) and arterial portography or splenoportography[7].

What are the treatment modalities of PVT and its complications?

Acute bleeding: In the acute setting, variceal banding or sclerotherapy, often requiring several sessions to obliterate the bleeding. This has a success rate of 95% for the acute bleed. Octreotide infusion has also been used in acute bleeding, with control of the acute bleed in 85% of patients. The rate of recurrent bleeding with this approach is 16 - 28%.

Anticoagulant therapy: Generally allows recanalisation of the thombosed veins in recently constituted

thrombosis. In the case of large oesophageal-gastric varicose veins that have never bled, treatment to prevent haemorrhages due to portal hypertension according to the same modalities as in cirrhosis must be associated with the prescription of an anticoagulant to maintain INR target range between 2 - 3. In the absence of prothrombotic affection or in patients having already suffered from haemorrhages due to portal hypertension, the benefit of anticoagulant therapy is less clearly established[8].

Thrombolysis: This approach is recommended in acute portal vein thrombosis through the transhepatic route, which avoids the need for systemic thrombolysis. Tissue-type plasminogen activator (tPA) has been used for this purpose with the dosage of 0.5 - 2.5 mg/h infused IV into portal vein through a catheter, followed by prolonged anticoagulation therapy for at least 3 months (indefinitely in patients with inherited coagulation disorders).

A nonselective beta-blocker – propranolol – reduces the risk of primary and recurrent variceal bleeding by decreasing portal pressure. It is indicated for primary and secondary prophylaxis of variceal bleeding with the dosage of 40 - 80 mg PO bid initially; titrate to 160 - 320 mg/d, according to heart rate (decrease to 25% below baseline) or hepatoportal venous gradient (HPVG) to less than 12.

Surgical care: In the setting of acute portal vein thrombosis with symptoms, shunt surgery with subsequent anticoagulation therapy is an alternative[9]. In general, shunt surgery is indicated when endoscopic treatment fails. A distal splenorenal shunt is usually the preferred surgical shunt. For patients in whom the splenic vein is also thrombosed and surgery is undertaken, splenectomy and other shunt procedures are done.

In portal vein obstruction, TIPS is indicated in uncontrollable variceal bleeding in a patient with cirrhosis, usually as a bridge to transplant. The choice of TIPS over shunt surgery depends upon the expertise of the centre in these techniques and the distance from skilled health care because TIPS is more likely to occlude and require revision. However, TIPS has the advantage of being less invasive than shunt surgery.

There were reports of treating unresectable massive type HCC with portal vein thrombosis by transcatheter arterial embolisation (TAE) and patients surviving more than 3 years[10].

Our patients, case 1 and 3, were treated conservatively with long-term anticoagulation; and in case 2, anticoagulation was withdrawn after two months since there was complete resolution of the thrombus. Pancreatitis most of the time is a self-limiting process. Thrombosis usually disappears and short-term anticoagulation limits the propagation of the thrombus.

What is the prognosis of PVT?

The specific aetiology of the portal vein obstruction not only influences the initial clinical presentation but also the time course and prognosis. PVT has an unfavourable influence on HCC prognosis. There are no therapy guidelines for HCC with PVT. According to the latest data, the mean survival is 18.2 months in patients without PVT and 5.1 months in PVT patients[5,6]. Our patient died within 5 months of diagnosis. Most frequently, PVT appears in late stages of HCC[11].

In liver cirrhosis there are many factors which create favourable circumstances for portal thrombosis, decreased portal flow and low levels of protein C, S and antithrombin III due to diminished synthesis. However, the studies published by now sustain that there are no differences between the levels of anticoagulant proteins (plasminogen, protein C, protein S or antithrombin III) among cirrhotic patients with or without PVT[12,13].

Portal vein thrombosis is a rare complication accompanied with acute pancreatitis or cholangitis/cholecystitis. Usually thrombosis shows spontaneous complete resolution in the following few weeks.

In the absence of cirrhosis, the 2-year bleeding risk from oesophageal varices is reported to be 0.25% and of those that bleed, the mortality rate is approximately 5%. Those with cirrhosis and varices have a 20 - 30% 2-year bleeding risk with a mortality rate of 30 - 70%. This difference is primarily a consequence of the normal hepatic function in the noncirrhotic patient.

In adults with portal vein thrombosis, the 10-year survival rate has been reported to be 38 - 60%, with most of the

deaths occurring secondary to the underlying disease (e.g., cirrhosis, malignancy). In children with portal vein thrombosis, the prognosis is much better overall, with a 10-year survival rate greater than 70%, which is attributable to the low incidence of underlying malignancy and cirrhosis.

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ROZAVEL F

CASE REPORT

JIACM 2011; 12(2):141-3

Langerhans Histiocytosis of Lung

KB Gupta, Vipul Kumar**, Ritu Aggarwal***,*

Abstract

Langerhans cell histiocytosis (LCH) can involve many organ systems. Primary pulmonary Langerhans cell histiocytosis (PLCH) is rare and is usually seen in young or middle-aged adults. Ninety per cent LCH show highlighting diagnostic signs on chest X-ray, high-resolution computed tomography and histology. Langerhans cell histiocytosis is overqrowth of cells of the reticuloendothelial system. This includes disorders previously called histocytosis X, including eosinophilic gramuloma, Hand -Schüller-Christian disease, and Letterer-Siwe disease.

Key words: Histiocytosis, Langerhans cell, lung.

Introduction

Langerhans cell histiocytosis (LCH) is a diverse group of clinical diseases in which a clonal population of cells with the phenotype of Langerhans cell accumulate in various tissues and cause damage. These disorders can involve many organ systems but primarily affect the bone, skin, lymph nodes, lungs, liver, spleen, endocrine glands, and nervous system. Primary pulmonary LCH is rare and is usually seen in young or middle-aged adults. It runs a clinical course distinct from multi-organ LCH. Ninety per cent of adults with LCH of the lung are smokers[1]. Tobacco smoke has been postulated to induce non-clonal hyperplasia of LCH cells, in which occasional clones may emerge. These proliferations often regress, failing to progress to autonomous neoplastic disease[2]. Chest X-ray appearances can vary from normal to reticulonodular shadowing and honeycomb fibrosis. Lung volume is normal, despite diffuse fibrosis. We report a case of LCH of the lung seen at our hospital.

Case report

A 35-year-old male patient was admitted to our hospital with cough, fever, breathlessness and streaking of blood of 20 - 25 days duration. He was a chronic smoker since the last 20 years, smoking 30 - 40 bidis per day. He did not have any significant past medical history. His appetite was normal and there was no history of weight loss. Physical examination was unremarkable. White blood cell count was 7.5 x 10^9/l and haemoglobin level 125 g/l. Renal and liver function tests were normal. Electrocardiography showed sinus rhythm, with a heart rate of 66 beats per minute; there were no ST changes. Chest X-ray showed predominantly micronodular shadows distributed over both lungs, some of them showing cavitations (Fig. 1). Lung volume was normal. Sputum analysis did not show any pyogenic organisms or acid-fast bacilli and no malignant cells were evident. Skeletal survey did not show any lesion. HRCT chest showed multiple thin-walled cysts of varying size and

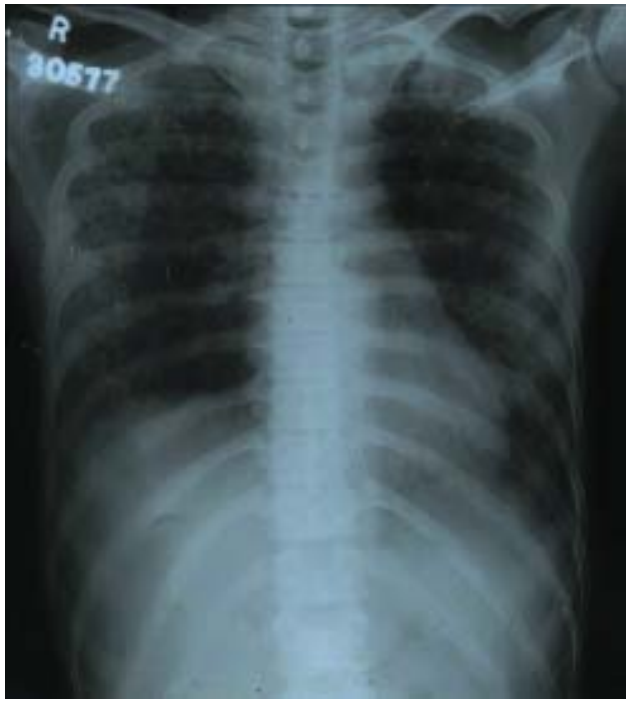

Fig. 1: *Chest X-ray PA view showing micronodular shadows distributed over both lung fields.*

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shape unevenly distributed on a background of micronodular lesions with concentration mainly in the upper- and mid-zones (Fig. 2). Basal portion of lungs was relatively spared. Areas of ground glass opacities were also seen in both lung fields. The findings were typical of pulmonary Langerhans histiocytosis X. Lung biopsy was advised but it was deferred because of the excessive surgical risk entailed.

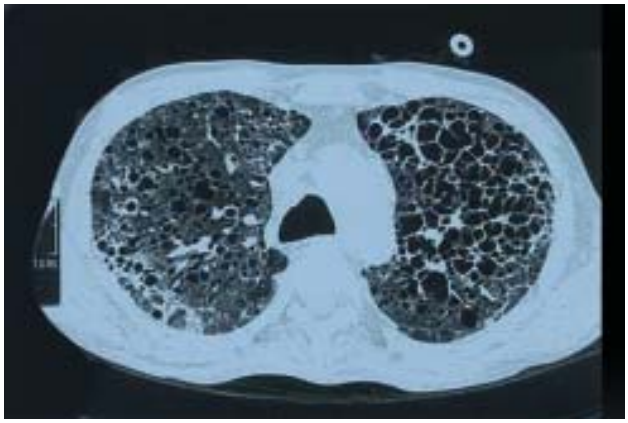

Fig. 2: *HRCT of chest showing multiple thin-walled cysts of varying size and shape unevenly distributed on a background of micronodular lesions.*

Discussion

Langerhan's cell histiocytosis is a rare disorder with an incidence of 10 cases per 2 million population as a whole. The annual incidence of pulmonary Langerhans histiocytosis X is estimated to be 1 - 2 cases per million population constituting 3% of interstitial lung disease[3]. The spectrum of LCH disease is wide. Single system disease can affect the skeletal system, skin, lung, or lymph nodes. Multi-system disease is associated with reticulo-endothelial system, liver or bone marrow dysfunction[4]. The clinical entities of LCH include Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma, and isolated LCH of the lung. Letterer-Siwe disease is a fulminant disease in children younger than 2 years, affecting the reticulo-endothelial system, bone, and lung. Hand-Schüller-Christian disease is an indolent disorder, affecting bone and lung, and resulting in diabetes insipidus, exophthalmos, and osteolytic skull lesions. Eosinophilic granuloma is a localised form of the disease, affecting bone or lung. Isolated LCH of the lung is a rare disease with no sex predilection and peak age incidence between 20 - 40 years[5]. Smoking is a predisposing factor. The patient may present with pulmonary or systemic symptoms or an asymptomatic radiographic abnormality.

LCH of the lung is one of the few diseases that present with normal lung volume despite diffuse fibrosis; it is difficult to make a diagnosis on the chest X-ray findings alone. Other conditions that present with similar chest X-ray findings include lymphangioleiomyomatosis, tuberous sclerosis, neurofibromatosis, sarcoidosis, constrictive bronchiolitis, and any interstitial disease associated with emphysema. High-resolution CT scanning can provide a confident diagnosis in most cases, even in the terminal stages of the disease[6]. It typically shows characteristic, small nodules (2 - 7 mm), diffusely distributed in the upper- and mid-zones of the lung, and sparing the lower zones. Nodules have centrilobular distribution. In a majority of patients nodules are associated with thick or thin walled cystic lesions and this pattern is highly suggestive of histiocytosis X[7]. As the disease evolves, cystic lesions become the predominant finding. Cysts are variable in size, usually less than 1 cm and may be confluent. Areas of ground glass opacities may be seen alongside nodules showing different stages of the disease in the same area. Pleural effusion and lymphadenopathy are extremely rare. Biopsy is indicated in cases where HRCT is inconclusive. Lung function studies may be normal, or show a restrictive, obstructive, or mixed pattern.

Histologically, the Langerhans cell is a pathologic cell type derived from the monocyte-macrophage line. The earliest lesions detected in LCH of the lung are interstitial accumulations of Langerhans cells with eosinophils in the submucosa and interstitium of the bronchioles. These lesions progress to discrete, symmetric nodules, usually with a fibrotic centre, with cellular peripheral interstitial tentacles. Langerhans cells have a moderately abundant cytoplasm and a medium-sized, folded, indented or lobulated nucleus with an elongated central groove producing a coffee-bean appearance. Characteristically, these cells express CD1a antigen and S-100. The peculiar rod-shaped organelles of Langerhans' cells are viewed on electron microscopy as Birbeck granules.

The natural course of isolated LCH of the lung is variable. Corticosteroid therapy is indicated when there is progressive loss of lung function. Long-term steroid therapy in the early stages has been reported to prevent progression of the disease in the majority of cases[8]. A

peculiarity of LCH of the lung is that features of the disease may change independently of each other, such as the resolution of radiographic signs despite the persistence of symptoms, and vice versa. The prognosis for pulmonary LCH in multisystem histiocytosis X disease is dependent on the extent and severity of extra-pulmonary disease. Vassallo *et al*[9] reported a median survival for patients with pulmonary LCH of 4 years, with 74% surviving 5 years, and 64% surviving 10 year.

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CASE REPORT

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Acute Ischaemic Hepatitis Caused by Seizures

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Abstract

Ischaemic hepatitis is a consequence of reduced blood flow into the liver due to acute hypotension caused by low cardiac output or shock of various aetiology. We present a case of the 29-year-old patient who had been successfully treated in the past for generalised tonic-clonic seizures and now presented with relapse. He developed acute ischaemic hepatitis due to seizures (all other aetiological factors were excluded) after one day of admission and recovered completely from it within two weeks. This case is being reported as seizures are a rare aetiological factor for causing acute ischaemic hepatitis.

Key words: Ischaemic hepatitis, Seizures

Introduction

Gibson and Dudley first published a paper an ischaemic hepatitis in 1824[1,2]. Ischaemic hepatitis is a consequence of liver hypoperfususion due to acute heart failure, shock of different aetiology, and/or passive organ congestion[3]. Acute systemic hypotension lasting more than 24 hours with systolic pressure below 80 mmHg initiates hepatocellular damage[4]. The basic morphological change is a massive centrlobular necrosis due to hepatic hypoxia, free oxygen radical damage, and preservation of the periportal zone[4].

The clinical features of ischaemic hepatitis resemble acute viral or toxic hepatitis with serum transaminases rising up to 100 times of normal, and similar increase in lactic dehydrogenase (LDH) is striking as well[5], but alkaline phosphatase remains normal. This condition is reversible if liver hypoperfusion is restored within 72 hours[6] but longer duration leads to more severe liver damage and worse prognosis[7].

Case report

A 29-year-old male had his first episode of generalised tonic-clonic seizure at the age of 5 years for which he was started on antiepileptic therapy despite which he again had a fit at 10 years of age. He remained seizure free even after withdrawal of antiepileptics 3 years ago; but now he presented with repeated episodes of GTCS lasting for half an hour of total duration. He was admitted in the ICU and was dilantinised. The baseline routine investigations, liver function tests and ultrasound abdomen were essentially normal but the CECT scan of the brain revealed a tiny calcified lesion in the parasaggital area of the left parietal lobe posteriorly. The transaminases and LDH started to rise within 24 hours of admission and reached a peak in 72 hours (AST and LDH > 25 ULN, ALT > 10 ULN with ALT/LDH ratio of 0.05). On sixth day of admission, all the liver enzymes showed downward trend and normalised wthin two weeks, alkaline phosphatase levels as expected in acute ischaemic hepatitis remained normal throughout the course of his illness. His viral and autoimmune markers, haemolytic profile, serum copper and ceruloplasmin levels were non contributory. He was discharged after two weeks of admission in a stable condition on antiepileptics and till date is asymptomatic. Our case is exceptional in view of seizures being a rare aetiological factor for causing acute ischaemic hepatitis.

Discussion

Ischaemic hepatitis (hypoxic hepatitis, acute hepatic infarction, post-traumatic hepatic insufficiency, shock liver) is not a common disease. It is particularly frequent in coronary units where it affects 22% of those with low cardiac output[3]. This disorder is documented in the intensive care units in 0.16 - 0.50% patients in total[8]. Ischaemic hepatitis is associated with a decrease in cardiac output due to heart failure, hypovolaemic (traumatic, haemorrhagic) shock, severe dehydration, pericardial tamponade, cardiorespiratory arrest, open heart surgery, asphyxia, prolonged seizures, heatstroke, interruption of hepatic blood flow during tumour resection. Haematological diseases (sickle-cell anaemia)

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can lead to occlusion of hepatic artery thus leading to hepatic hypoperfusion too[4]. The most frequent cause of ischaemic hepatitis is left-sided heart failure because of coronary artery disease and/or cardiomyopathy when hypotension or reduced heart output develops[9]. The reduction of the systolic volume < 50% leads to hepatic ischaemia due to reduced blood flow through coeliac axis and portal vein[10]. Mechanisms of liver damage are related to severity and duration of the fall of blood pressure[11]. Marked hepatic arterial and portal vein vasoconstriction may further reduce liver perfusion more than 70% thus representing an important contributing factor to hypoxic/anoxic hepatocellular injury[12].

Increased oxygen extraction by the liver in situations of low hepatic blood perfusion ensures constant oxygen consumption within the limits of hepatic flow. A reduction in hepatic flow greater than 70% results in decreased oxygen uptake. In significant hypoperfusion states and shock, hepatic arterial vasospasm and intense splanchnic vasoconstriction markedly augment hypoxic liver damage. In chronic respiratory diseases, elevated aminotransferases and microscopic changes of hepatocellular hypoxic damage are detected when blood oxygen saturation is < 35% even if cardiac index is normal, indicating that liver damage may occur primarily as a result of hypoxia[13]. This is further supported by liver hypoxic damage in Pickwick syndrome, where there is neither hypotension nor heart failure[14]. Cellarier *et al* have defined ischaemic hepatitis as a cardiac liver[16]. Shock and hypotension during variceal bleeding in liver cirrhosis rarely lead to ischaemic hepatitis because of decreased hepatic metabolism and lowered liver sensitivity to hypoxia[17]. Greater clinical application of splanchnic vasoconstrictor drugs vasopressin and somatostatin in variceal haemorrhage may potentially change this balance by further increasing splanchnic hypoperfusion and promoting hepatic ischaemia[18].

In ischaemic hepatitis, laboratory abnormalities are very important[4, 9]. After the initial insult, marked and rapid elevation of serum transaminases especially AST, occur within 24 to 48 hours. Their return to normal depends on the duration of liver ischaemia. Serum concentrations decrease to normal in 3 to 11 days if perfusion and oxygenation are restored and urine output is normal. A similar rise and fall of serum LDH concentration occurs because of liver hypoperfusion and metabolic acidosis. This helps in differentiating ischaemic from viral hepatitis where LDH is mildly increased only[7, 8]. Alkaline phosphatase generally remains normal. Serum bilirubin may occasionally rise but is rarely greater than four times the upper limit of normal. This pattern of biochemical changes was seen in our patient with a striking increase in serum aminotransferases and LDH while alkaline phosphatase was normal. Markedly elevated levels of aminotransferases are seen characteristically in patients with acute left heart failure, acute worsening of severe chronic congestive cardiac failure, hypotension or shock. AST tends to be higher than ALT, due to the AST-rich cardiac myocytes[19,20]. An increase of AST appears earlier than the increase in ALT. If the elevation in AST is due to cardiac failure or circulatory shock, the level is falling within days of circulatory improvement. In contrast, high AST level usually persists in cases of viral or drug-induced hepatitis and is independent of improvement of circulatory status. Beside ischaemic hepatitis, very high levels of AST can be found in patients with drug-induced or viral hepatitis also, but ALT levels are usually higher in the latter. In our patient, AST concentration was 60 times higher than normal what with negative viral markers and the exclusion of toxic liver damage which suggested ischaemic hepatitis. The differential diagnosis between ischaemic hepatitis and acute hepatitis is not easy, especially if heart failure, hypotension, and shock are present in the acute viral hepatic illness. Definite diagnosis of ischaemic hepatitis is based on liver biopsy if the general condition and haemostasis status allow. Coagulative centrilobular ischaemic necrosis of hepatocytes without significant inflammation is the characteristic morphological change[7].

The outcome of the disease is poor if the cause of hypotension and liver anoxia is not corrected[4,10,12]. In ischaemic hepatitis, prognosis depends on the cause of hypotension and the patient's cardiovascular status. The disease is often mild, and sometimes is not even diagnosed. Long-lasting liver hypoperfusion or circulatory failure superimposed on an already damaged liver and associated diseases of the other organs may, in turn, cause fulminant hepatitis and have a bad prognosis[6,8].

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CASE REPORT

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Rifampicin-induced Thrombocytopenia – A Rare Presentation

*Amol Chandra**

Abstract

One of the rarest but potentially life-threatening complication of certain anti-tubercular drugs is thrombocytopenia (TCP). Rifampicin is one such drug associated with the causation of thrombocytopenia. A case of rifampicin-induced thrombocytopenia is presented for the simple reason of its rarest occurrence and documentation.

Introduction

Thrombocytopenia (TCP) is a well-known complication following the administration of different drugs and is characterised by accelerated platelet destruction whenever the offending drug is taken by the sensitised individual[1]. Destruction may be mediated by a non-immunologic or immunologic mechanism. The latter is associated with drug-induced thrombocytopenia. Immunologically mediated mechanisms of platelet destruction are often based on generation of antibodies directed against platelet membrane or to various immunogens whose antibodies cross-react with platelet moieties[2]. These platelets are subsequently removed by monocyte-macrophage in the spleen and liver. Drugs that are known to cause TCP are quinine, quinidine, chloroquine, sulphonamides and related drugs (tolbutamide and chlorothiazide), digoxin, meprobamate, sedatives, anti-convulsants, methyldopa, penicillamine, amphotericin, asprin, etc.

Case report

A 16-year-old female, was admitted to the Department of TB and Chest Diseases, SN Medical College, Agra, with the chief complaints of low-grade fever, cough with expectoration for 1 year, decrease in appetite for 7 months and skin eruptions for 2 days. The patient was on four anti-tubercular drugs for 7 days i.e., rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) which were prescribed by a medical practitioner. Detailed clinical examination of the patient revealed purpura on the face, arm, and forearm. All the anti-tubercular drugs were stopped immediately.

At the time of her presentation, a clinical suspicion of rifampicin-induced thrombocytopenia was made and the patient was investigated accordingly. Haemoglobin of the patient was 7.5 gm%, TLC - 13,700 cells/mm^3, DLC - P_{74} L_{26}, bleeding time was 2 min 15 sec and clotting time was 6 min and 10 sec, blood urea - 24 mg%, S. creatinine - 0.9 mg%, SGOT - 28 IU/L, SGPT - 22 IU/L, random blood sugar - 96 gm%, platelet count - 18,000/mm^3, and anti-nuclear antibodies were negative.

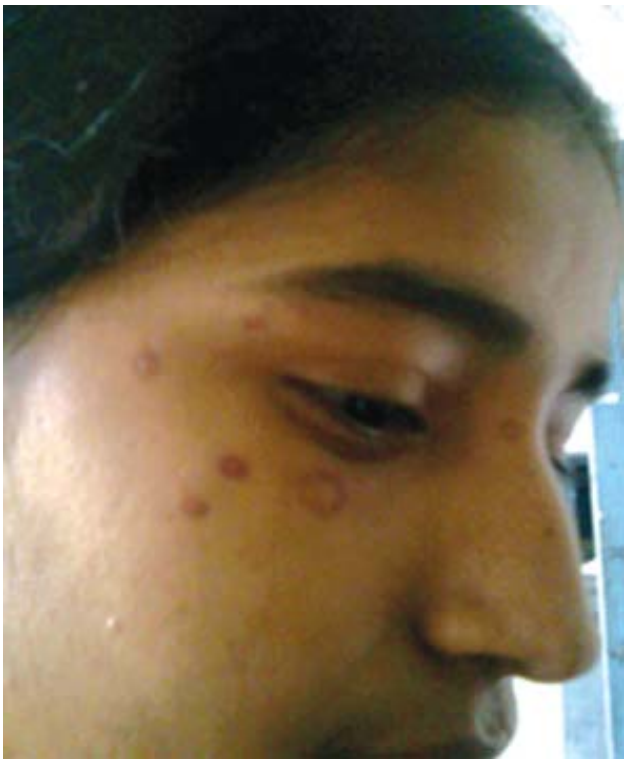

Fig. 1: *Showing purpura on the face below the right eye of the patient.*

Chest X-ray revealed consolidation in the left lower lung zone. Her sputum smear was positive for AFB by Ziehl-Neelsen staining.

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Fig. 2: *Showing purpura over the left forearm.*

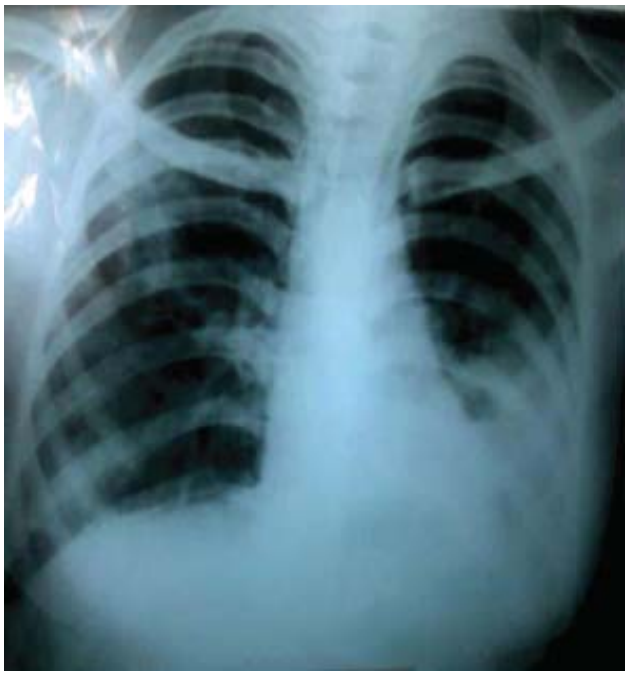

Fig. 3: *Showing consolidation in the left lower lung zone.*

The patient was managed conservatively. A total of 2 units of blood were infused. After 5 days of treatment her haemoglobin was 9.5 gm%, TLC - 8,000 cell/mm^3, DLC - P_{65} L_{33} E_{00} M_{01} and platelet counts returned to 1,50,000/mm^3. Along with this the patient also improved symptomatically. Later on, after informed consent, streptomycin, ethambutol, isoniazid and pyrazinamide were started gradually. There were no complications and her platelet counts remained normal. All her haematological investigations were monitored regularly during her hospital stay and she was discharged on the same regimen.

Discussion

Adverse reactions to rifampicin are uncommon on daily regimen, but are relatively common with an intermittent regimen[3]. These include an abdominal syndrome, a cutaneous syndrome, a flu syndrome, purpura, and elevated serum transaminases. Thrombocytopenia is an adverse reaction associated with the intermittent rifampicin regimen[4]. Our patient had TCP on daily regimen which was restarted 4 months after she had last received rifampicin. Rifampicin was stopped after a clinical suspicion of thrombocytopenia.

The use of rifampicin may produce immune-mediated thrombocytopenia. Antibodies of IgG and IgM type have been demonstrated in many of these patients. Thrombocytopenia has been more frequently observed when twice weekly regimen of 900 mg of rifampicin was used, and it resolved with reduction of dose to 150 - 300 mg/day[5]. Isoniazid, pyrazinamide and streptomycin may also produce thrombocytopenia.

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CASE REPORT

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Inhaled Steroids: Hyperglycaemia – A Side Effect

Vikas Dhikav, KS Anand***

Case report

A 55-year-old female, diabetic for the last 15 years, presented in the Department of Neurology, Dr. Ram Manohar Lohia Hospital, New Delhi for the treatment of abnormal sensations in both lower limbs. She was taking tablet glimepiride 1 mg twice daily and tablet metformin 500 mg three times daily.

Upon taking her history, it was found that she was also an asthmatic and had been taking salbutamol inhaler and oral theophylline on 'as per need' basis. She further revealed that after taking 2 - 3 puffs of this inhaler, her blood sugar increased. At times, even a single dose had caused an increase in blood sugar. She had noticed it frequently during exacerbations of asthmatic symptoms when she had to take multiple puffs. We got this documented by getting her blood sugar estimated. We examined her on 15th March 2006 and her blood sugar levels were: fasting - 130 mg/dl, post-prandial - 170 mg/dl. On 30th March 2006, her blood sugar was 172 mg/dl fasting and 228 mg/dl post-prandial. During these last 15 days, she took about 10 puffs of the inhaler at different times. Her diet control, medications and exercise (morning walk for 20 minutes) remained unchanged.

Discussion

Aerocort® is a fixed-dose combination of salbutamol and beclomethasone dipropionate (50 microgram + 100 microgram per puff respectively). Salbutamol is a beta 2-adrenergic agonist and is a potent bronchodilator.

Beclomethasone is a synthetic glucocorticoid with potent anti-inflammatory activity and weak mineralocorticoid activity. This combination salbutamol and beclomethasone is used for patients who require regular doses of both drugs for treatment of their obstructive airways disease, e.g., asthma – mainly of the persistent type.

The side-effects of the combination are reflective of individual ingredients. Mild tremors, headache, hypokalaemia and muscle cramps occur. Beclomethasone causes oral thrush among many other side-effects. A case of hypoglycaemic episodes leading to seizures has been described[1]. Glucocorticoids use is associated with the risk of hyperglycaemia in patients without known diabetes mellitus, and worsening of glycaemic control in diabetic patients[2]. The effects of glucocorticoids on hyperglycaemia usually remit within 48 hours of discontinuation of oral administration. Salbutamol in doses up to 2.5 mg by nebuliser causes no clinically significant increases in blood glucose in diabetes or chronic renal failure patients[3]. Therefore, the observed hyperglycaemia is presumably due to the glucocorticoid component, i.e., beclomethasone. Glucocorticoids oppose insulin action and stimulate gluconeogenesis, especially in the liver, resulting in a net increase in hepatic glucose output. Most people can produce enough extra insulin to compensate for this effect and maintain normal glucose levels, but those who cannot, develop steroid-induced diabetes. Clinically significant systemic effects of the inhaled glucocortcioids are increasingly been recognised recently[4].

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CASE REPORT

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Vivax Malaria – Not Benign Anymore

*Rajesh Deshwal**

Abstract

Plasmodium vivax causing cerebral malaria has been reported rather frequently in children, but in adults it had been a rarity. Notwithstanding this now more and more reports are emerging implicating vivax as a cause of cerebral symptoms. A soldier presented with pyrexia of three days duration and abnormal behaviour of six hours duration. Clinical evaluation and investigations revealed Plasmodium vivax as the culprit. He was treated with artemisinin-based combination therapy successfully. The case is being presented to highlight the extended spectrum of presentation of the hitherto considered benign species of malaria along with review of literature.

Key words: Cerebral malaria, psychosis, Plasmodium vivax.

Introduction

Cerebral malaria is usually caused secondary to *Plasmodium falciparum* infection. *Plasmodium vivax* causing cerebral malaria has been reported in children rather often, but *P. vivax* in adult population causing cerebral malaria has been reported very infrequently.

Case report

A 42-year-old serving soldier presented with history of high-grade, intermittent fever of 3 days duration and abnormal behaviour of 6 hours duration. He denied any history of drug abuse, alcohol intake, psychotic disorder in the past. Clinical examination revealed a hyperexcitable and restless patient, hurling verbal abuses at the nursing staff and failure to recognise his colleagues. His temperature was 101° F, pulse 104/min, BP 130/80 mmHg. He had no pallor, icterus. Abdominal examination revealed spleen palpable 2 cm below left costal margin. CNS examination revealed no neck rigidity and no focal neurodeficit. Other systemic examination was unremarkable. Investigations revealed BT trophozoites in peripheral smear and antigen test was positive for *P. vivax* and negative for *P. falciparum*. Other routine haematological and biochemical parameters were within normal limits. The patient was treated with injectable artesunate-based combination therapy in appropriate dosages along with supportive therapy. The patient responded well with normalisation of behaviour within 8 hours of starting therapy and resolution of pyrexia over the next 24 hours. Blood smear became negative after 48 hours of therapy. Oral primaquine was given for radical cure in appropriate dosages.

Discussion and review of literature

Plasmodium vivax causing cerebral malaria, thrombocytopenia, disseminated intravascular coagulation (DIC), ARDS, and renal failure has been reported sparingly in the last 30 years. The first case of psychosis due to *Plasmodium vivax* malaria, imported from India was reported from Trinidad in 1996. Tilluckdharry *et al*[1] reported a 44-year-old Trinidadian male who presented with fever and psychotic episodes in association with vivax malaria. The symptoms of both malaria and psychosis were resolved following the standard chloroquine-primaquine therapy. Three cases of *Plasmodium vivax* malaria (all adult male patients) complicated by seizures and symptoms of diffuse meningoencephalitis were reported rather recently by Sarkar *et al*[2]. Two patients had predominantly meningeal signs, while in the third patient the features were purely of encephalitis. All cases were treated with artesunate. Published reports by various authors[3-16] have found presentations ranging from seizures, decreased level of consciousness, aphasia, hemiparesis, delirium, coma, stupor, psychosis associated with *Plasmodium vivax* infection. Kochar *et al*[18] reported 11 cases of severe *Plasmodium vivax* malaria in Bikaner (western India). Patients exhibited cerebral malaria, renal failure, circulatory collapse, severe anaemia, haemoglobinuria, abnormal bleeding, acute respiratory distress syndrome, and jaundice. Peripheral blood microscopy, parasite

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antigen-based assays, and parasite 18s rRNA gene-based polymerase chain reaction (PCR) showed the presence of *P. vivax* and absence of *P. falciparum*.

hemostasis and mechanical obstruction leading to pathogenesis. The events resulting in the development of cerebral malaria complications are multi-factorial,

Table I: Literature cases of cerebral malaria caused by *Plasmodium vivax*.

Author (Reference)	Year	No of case(s)	Patients age (years)	Location of cases	Neuropsychiatric features
Rossle[4]	1921	1	21	NS	NS
Bruetsch[5]	1932	1	61	United States	No CNS features
Dhayagude[6]	1943	7	NS	India	NS
Tarejev[7]	1943	12	4 - 17	Russia	All with seizures and decreased levels of consciousness
Boshes[8]	1947	1	26	Italy	Decreased level of conciousness; seizures; visual loss
Hill[9]	1962	1	32	United States	Aphasia; hemiparesis
Roder[10]	1967	1	18	Africa	Decreased level of consciousness
Verma[11]	1976	3	3.5, 7, 9	India	Coma; seizures; delirium and aphasia
Gopinathan[12]	1982	2	Adults > 18	India	NS
Sachdev[13]	1985	6	4 - 12	India	Coma; seizures; hemiparesis
Arora[14]	1988	1	28	India	Coma; seizures
Valecha[15]	1992	2	2 and 3	India	Coma; seizures
Islam[16]	1995	1	30	Pakistan	Stupor
Tilluckdharry[1]	1996	1	44	India*	Confusion; psychosis
Beg[3]	2001	1	60	Pakistan	Seizures; confusion
Sarkar[2]	2008	3	Adults > 18	India	Seizures; features of diffuse meningoencephalitis
Deshwal (present case)	2010	1	42	India	Confusion; psychosis

*NS = not stated; * The case occurred in Trinidad: was imported from India.*

A unifying hypothesis[17] for the genesis of cerebral malaria proposes that parasite antigens (released by replication in blood, surface molecules on parasitised erythrocytes, or merozoites) activate platelets that, in turn, contribute to the activation of the inflammatory response and increased levels of endothelial cell adhesion molecules (eCAMs). Increased levels of eCAMs result in further parasitised-erythrocyte sequestration and marked local inflammation that might disrupt the brain microvasculature, which cannot be repaired by the haemostasis system because of its procoagulant state. Disruption of the brain microvasculature can result in vascular leak and/or haemorrhage into the brain; similar processes can occur in other vascular beds, including the lung.The blockage of functional capillaries by parasitised and/or unparasitised erythrocytes with decreased deformability or rosettes is also a key interaction between encompassing a dynamic interaction between three processes, thereby explaining the complexity of this deadly syndrome.

Plasmodium vivax, as has been traditionally believed,is no longer a benign species and is causing presentations akin to *P. falciparum*. It is imperative that clinicians are aware and are ready to handle the complications caused by *Plasmodium vivax* which have been traditionally associated with *P. falciparum* malaria.

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CASE REPORT

JIACM 2011; 12(2):153-4

A Rare Variant of Ramsay Hunt Syndrome

*AK Gupta**

Abstract

Ophthalmic zoster is due to severe herpetic infection of the geniculate ganglion of the trigeminal nerve, whereas infection of lesser severity leads to Ramsay Hunt syndrome. In Ramsay Hunt syndrome, this swollen ganglion exerts pressure over the facial nerve and presents in the form of infra-nuclear palsy and loss of taste sensation with eruptions over the anterior two-third of the tongue, often associated with V, IX, and X cranial nerves palsies, and rarely associated with vestibulitis and cochleitus.

On the contrary, reverse to this classical syndrome, i.e., a case with gross involvement of superior ganglion of vagus (X) nerve (somatosensory component), i.e., eruption over the external ear and exerting pressure over the glossopharyngeal (IX) nerve (motor component only), i.e., involvement of stylopharyngeus muscle presents in the form of difficulty in swallowing, with minimal involvement of geniculate ganglion of the trigeminal nerve, i.e., infra-nuclear facial nerve palsy is reported. Though available literature was reviewed, this rare variant is not reported so far.

Introduction

One of the commonest, Ramsay Hunt syndrome, is due to herpetic infection of the geniculate ganglion of the trigeminal nerve exerting pressure over the facial nerve, often associated with V, IX, and X cranial nerves palsies and rarely associated with vestibulitis and cochleitus. Clinically, the patient presents with infra-nuclear facial palsy and loss of taste sensation with eruptions over anterior two-third of the tongue. Rarely these eruptions extend over to external ear (concha, ante-helix, tragus, external auditory canal, and lateral surface of the tympanic membrane). This little bit involvement of the external ear depends on the connection between auricular branch of facial and vagus nerve in the petrous bone[1].

Involvement of IX and X cranial nerves clinically manifests in the form of difficulty in swallowing. The involuntary phase, i.e., the second phase, of swallowing is complex; it is mainly controlled by the glosspharyngeal (IX) and vagus (X) cranial nerves. The only muscle supplied by the IXth nerve is stylopharyngeus, which lifts the larynx forward; therefore, in isolated IXth nerve lesion, food tends to fall into the larynx, gives a sense of choking. Vagus elevates the soft palate, occludes the nasopharynx, flips the epiglottis and dilates the hypopharynx. Thus in isolated vagus nerve lesions, food regurgitates to the nostrils, falls into the larynx and pools into the hypopharynx[2].

Case report

A 75-year-old non-diabetic, non-hypertensive female, presented with sudden onset of right facial weakness, choking sensation on swallowing (without any nasal regurgitation) and burning sensation over the right external auditory meatus for the last two days. Her bowel and bladder habits were normal.

On examination, she was afebrile, anaemic, pulse was 76 per minute, BP was 126/84 mmHg. Maculo-papular eruptions over the right ante-helix, tragus and postero-superior surface of external auditory canal were present. CNS: Higher mental functions and speech were normal. Among the cranial nerves, except for right infra-nuclear facial palsy, all others were normal, i.e., movements of soft palate and vocal cords were normal. Gag (pharyngeal) reflex was normal, somatic and taste sensations in the oral cavity, tongue and pharynx were normal. No other neurological deficit was observed. Other systemic examination was non-contributory. Haemogram, blood biochemistry, X-ray chest, ECG, and USG abdomen were normal.

In the present case, neurological deficit (a) right facial weakness including forehead, sparing taste sensation and without vesicular eruptions over anterior 2/3 of tongue, suggest infra-nuclear involvement of the right seventh nerve (motor component only); (b) some sense of choking and slight initial difficulty in swallowing, without nasal

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regurgitation, dysphonia and aspiration may suggest isolated involvement of the glosspharyngeal nerve (motor component), which is very rare; (c) distribution of eruptions over right ante-helix, tragus, postero-superior surface of external auditory canal and postero-superior part of lateral surface of tympanic membrane, suggests involvement of right vagus nerve without nasal regurgitation and aspiration (somatic sensory component only).

The patient was managed indoor with naso-gastric feeding, antibiotics, and anti-inflammatory analgesics. On the next day, the maculo-papular eruptions turned to vesicles and pustules, further extended to the postero-superior part of the lateral surface of the tympanic membrane, followed by perforation on the next day. Acylovir was started and within a week the eruptions disappeared with slight improvement in swallowing. By the end of three weeks her swallowing and facial weakness recovered completely.

Discussion

In this reported case, involvement of (a) motor component of right facial (sparing taste over tongue), (b) motor component of right IXth nerve (sense of choking, sparing taste and somatic sensation over tongue and soft palate), and (c) somatic sensory component of right vagus (extensive eruption of right external ear without nasal regurgitation, dysphonia and aspiration). It is difficult to explain all the three deficits due to herpetic infection of isolated geniculate ganglion alone. Probably in this case, the superior ganglion of the right vagus was mainly infected with mild infection of the right geniculate ganglion (contrary to the commonest involvement) which can explain all the deficits.

Gross involvement of the right superior ganglion of the vagus nerve, presented with somatic sensory symptoms and vesicular lesions over its sensory distribution and further exerted pressure over the right IXth nerve in the jugular foramen presented in the form of a sense of choking. Mild infection of geniculate ganglion was unable to produce eruptions over the tongue; at the same time, this swollen ganglion exerted pressure over the motor fibres of the facial nerve and manifested in the form of facial palsy. Reduction in this inflammatory swelling of the superior ganglion of the right vagus and right geniculate ganglion decreases the pressure over the IXth and VIIth cranial nerves respectively, thereby improving these neurological deficits. Such type of neurological involvement was not found in the literature, therefore it is being reported here.

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CASE REPORT

JIACM 2011; 12(2):155-8

Role of Cardiac Magnetic Resonance Imaging in Evaluating New-onset Heart Failure

Michele Murphy, Gyanendra K Sharma***

Abstract

In the United States of America, blacks have a higher prevalence of heart failure and become symptomatic at younger ages[1-4]. This is a result of higher prevalence of hypertension, obesity, diabetes, systolic dysfunction, and left ventricular hypertrophy. Cardiac amyloidosis is an unusual cause of heart failure in the young, with less than 3% occurring below 40 years, and 4.3% affect African Americans[5]. Delayed gadolinium-enhanced cardiac MRI has a sensitivity of 80% to detect amyloidosis and can obviate the need for a myocardial biopsy. This case highlights the significance of early echocardiographic evaluation in the work-up of new onset heart failure. Further evaluation by a gadolinium-enhanced cardiac MRI for infiltrative cardiomyopathy may have therapeutic and prognostic implications.

Key words: Cardiac amyloidosis, CHF.

Introduction

Cardia study revealed racial differences in the incidence of heart failure, being more common among blacks[6,7]. Most notably, heart failure occurred at a relatively young age and was largely dependent on the presence of hypertension, obesity, chronic kidney disease and systolic dysfunction, and left ventricular hypertrophy[1,4.]

Primary systemic amyloidosis is a rare disease within the spectrum of plasma cell disorders commonly diagnosed at a median age of 59 years, of which only 3% of patients are < 40 years of age and 4.3% are African Americans[5]. It has associated features of fibril protein deposits, immunoglobulin light chain derived, similar to that seen in myeloma amyloidosis, but without overt myeloma. Often times presentation is highly varied, with most clinical manifestations primarily affecting the kidneys, heart, peripheral nerves, and bone marrow[5, 8, 9].

Case

A 45-year-old African American man presented to the emergency department for dyspnoea of one month. He reported being well until having a recent viral respiratory illness, several days previously and progressing to where he had to stop while walking even for a few yards due to severe shortness of breath. He had 2-pillow orthopnoea, bilateral lower extremity swelling, paroxysmal nocturnal dyspnoea, and abdominal pain. He denied any fever, chills, nausea, vomiting, diarrhoea, chest pain, and diaphoresis.

He had a past medical history significant for asthma, left pneumothorax, splenectomy, and no significant family history.

On physical examination, significant findings consisted of bilateral jugular venous distention and 3+ pitting oedema of the lower extremities. He had a normal cardiac examination without S3/4 gallop, and bilateral basal rales.

Laboratory data revealed low normal haemoglobin/haematocrit (12.4 gm/dl/37.1%), normal platelets, normal coagulation studies, normal renal and liver function tests. Chest X-ray revealed cardiomegaly and pulmonary oedema. ECG showed normal sinus rhythm with no ST- or T-wave abnormalities.

He was admitted to the hospital for decompensated heart failure, with initial signs and symptoms of dyspnoea, lower extremity oedema consistent with volume overload, elevated JVP and started on frusemide for diuresis. His respiratory status improved markedly during the hospital course with resolution of his dyspnoea and oedema. A TTE revealed a left ventricular ejection fraction (LVEF) of 50%, moderate left ventricular hypertrophy (LVH), biatrial enlargement, increased right ventricular size, small global pericardial effusion, and restrictive diastolic filling pattern with speckled appearance of the myocardium, suggestive of an infiltrative cardiomyopathy (Fig. 1, 2). Delayed

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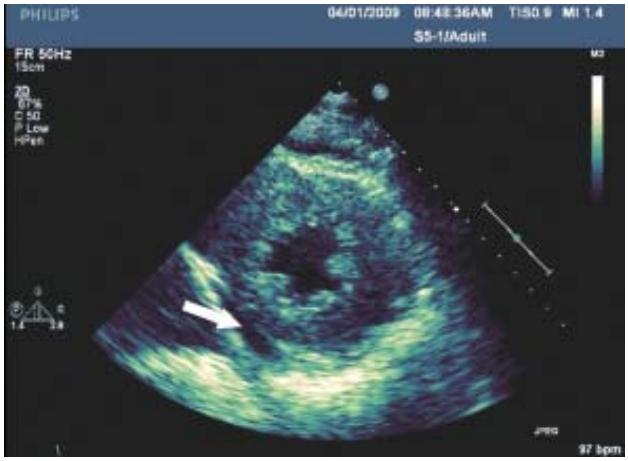

Fig. 1: *Parasternal short axis view: LVH, pericardial effusion (arrow).*

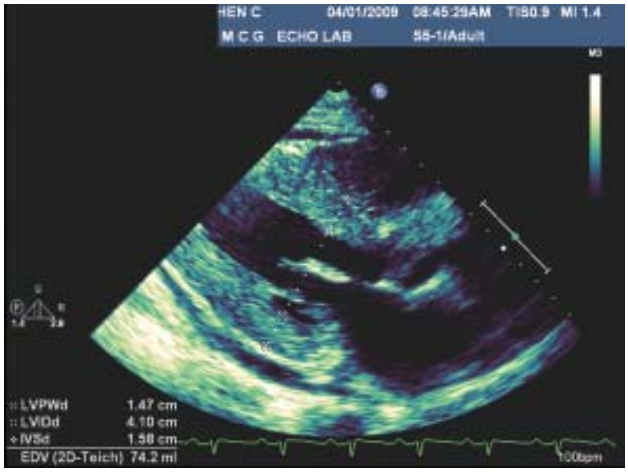

Fig. 2: *Parasternal long axis view: Speckled appearance of myocardium, LVH.*

Gadolinium-enhanced cardiac MRI showed lack of suppression (nulling) of myocardial signal despite changing TI time, findings highly suggestive of cardiac amyloidosis (Fig. 3).

Further work-up was done including SPEP and UPEP to screen for amyloidosis. The SPEP was without protein spike, UPEP unable to be completed due to low proteinuria. He also underwent a subcutaneous fat biopsy which was Congo red positive, consistent with amyloidosis. At the time of discharge he was optimised on his medication for heart failure.

Further out-patient work-up of his amyloid was done including a bone marrow biopsy showing moderate increased plasma cells (12 - 25%) with lambda light chain restriction, no lymphocytic infiltrate or lympho-plasmacytoid infiltrate seen. SPEP showed decreased albumin, no m-M spike identified. A skeletal survey was done which was without any lytic lesions. Cytogenetic FISH analysis of the bone marrow was done which was without evidence of clonal abnormalities as seen in MM. Flow Cytometry analysis revealed a small population of plasma cells expressing lambda light chain restriction, consistent with plasma cell dyscrasia. SPEP revealed 47.8 lambda free light chains.

Discussion

AL clinically presents at a median age of 60 - 69 years, with

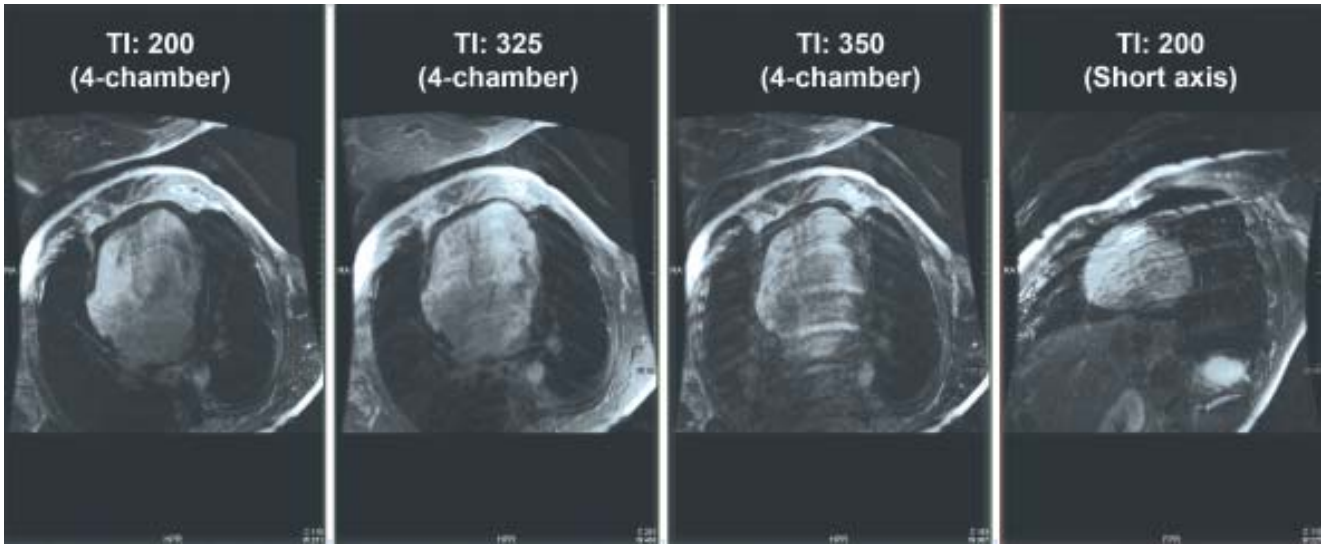

Fig. 3: *Delayed Gadolinium-enhanced MRI: Failure to null myocardium.*

less than 3% younger than 40, and 4.3% African American[5]. It is well known that the factors influencing prognosis consist of advanced age, plasma cell morphology, and cytogenetics, and in AL amyloidosis, the degree of cardiac involvement, with clinically evident heart failure being the main cause of cardiac death. In patients with primary cardiac amyloidosis, the mean survival is 13 months, with rates varying depending on associated symptoms: 4 months after onset of heart failure[11].

Diagnosis of cardiac amyloidosis or an infiltrative cardiomyopathy begins with early electrocardiographic (ECG) findings of lack of left ventricular hypertrophy and biatrial enlargement. Typical TTE features of restrictive cardiomyopathy include left ventricular hypertrophy, reduced left ventricular ejection fraction, restrictive diastolic filling pattern and disproportionate atrial enlargement to ventricular enlargement. Cardiac MRI has emerged as an important tool in the evaluation and diagnosis of a patient with infiltrative cardiomyopathy.

Amyloid cardiomyopathy has characteristic MRI findings. Widespread enhancement of the thickened myocardium on delayed post-contrast inversion recovery T1-weighted is the main finding on cardiac MRI. By using a delayed gadolinium-enhanced imaging technique, this requires the selection of an appropriate inversion time, the time needed from the administration of contrast medium and imaging to null the signal from normal myocardium. As the time delay between contrast administration and imaging increases, the inversion time must also be increased. Normal myocardium is nulled and appears black on delayed imaging. In infiltrative cardiomyopathies, even with the correct inversion time selected, suppression of signal from normal myocardium is not achieved. Due to a combination of increased volume of distribution in fibrosis, protein deposition and slower washout kinetics, there is a relative accumulation of gadolinium in areas of expanded extracellular space in comparison with normal myocardium, which can be detected in the late washout phase during delayed enhanced imaging[12]. This is often times misinterpreted as a technical error. However, recognition of this along with clinical history and echocardiographic findings should prompt recognition of a diffuse infiltrative process.

Delayed hyperenhanced cardiac magnetic resonance (DHE-CMR) imaging technique has emerged as an important diagnostic tool. The DHE-CMR in patients with amyloidosis has a sensitivity of 88%, specificity 90%, positive predictive value 88%, and negative predictive value 90%, and it is a positive predictor of 1-year mortality[12]. This can potentially obviate the need for further invasive endomyocardial biopsy for amyloidosis.

Conclusion

This case highlights the significance of early echocardiographic evaluation in the work-up of new-onset heart failure. Unexplained left ventricular hypertrophy with speckled appearance should prompt further cardiac MRI evaluation for infiltrative cardiomyopathy especially amyloidosis, even in young individuals. Early diagnosis and appropriate therapy may have significant prognostic implications.

Appendix

ECG: Electrocardiogram

TTE: Transthoracic echocardiogram

MRI: Magnetic resonance imaging

DHE MRI: Delayed hyperenhanced myocardial resonance imaging

LVH: Left ventricular hypertrophy

SPEP: Serum protein electrophoresis

UPEP: Urine protein electrophoresis

FISH: Florescent in situ hybridisation

AL: Cardiac amyloidosis

MM: Multiple myeloma

TI: Time to image

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CASE REPORT

JIACM 2011; 12(2):159-61

Munchausen's Syndrome – A Rare Presentation

Ravinder Garg, Simmi Aggarwal**, KS Kajal****

Abstract

Munchausen's syndrome is one of the most intriguing of factitious disorders where the disease is created. In our case the patient created the disease in an atypical way by pricking herself with pins in the breast which were detected by imaging techniques.

Key words: Syndrome, factitious.

Introduction

Munchausen's syndrome is a severe and chronic form of factitious disorder where a person creates the symptoms of illness in order to draw attention or sympathy. The individual may self-administer a drug or other material to create physical signs. The action is deliberate. We present one such case of the rare and atypical presentation of this syndrome.

Case history

Our patient, a 24-year-old matriculate female married for the last 6 years and having one 5-year-old daughter, presented with a one-month history of pain in the left breast. It was a constant, non-radiating, and mild-to-moderate degree pain with no precipitating or relieving factors. There was no symptom pertaining to the CVS, respiratory, GI system or CNS, and there was no history of any lump in the breast. Examination revealed mild pallor and scars on both the forearms and abdomen. There were three scars (2 - 4 cm) on the right forearm, 3 scars (2 - 3 cm and 'M' shaped) on the left forearm, 3 scars (9 cm, 4 cm, and 2 cm) on the right-side of abdomen, and 6 - 7 scars (2 - 4 cm) on the left-side of abdomen (Fig. 1a, 1b, 1c). There was no tenderness or lump in the left breast. Rest of the examination did not reveal any abnormality. Her laboratory investigations revealed haemoglobin of 9 gm% with the rest of the profile being within normal limits. X-ray of the chest (PA and left lateral view) showed 3 dense radio-opaque foreign bodies suggestive of pins in the left breast (Fig. 2a, 2b). Abdominal ultrasonography was normal and X-ray of both the forearms was also normal. She was sent for CT scan of the chest which showed three linear hyper-dense foreign bodies in the chest wall (corresponding to the marks on X-ray chest) (Fig. 3).

On further questioning, the patient revealed that she had self pricked and inserted 3 drawing pins in the left breast 3 years back. She had family problems and strained

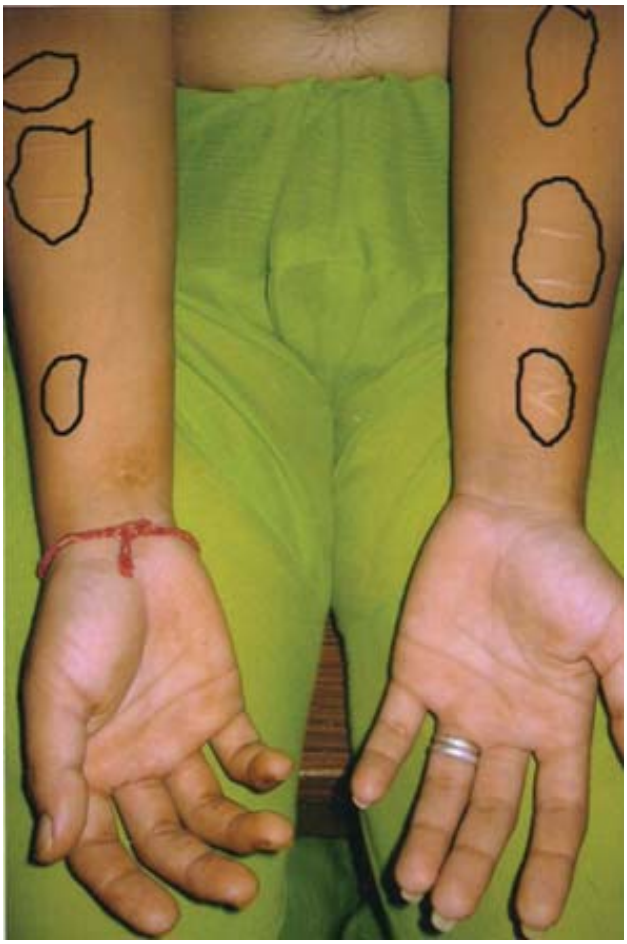

Fig. 1a:

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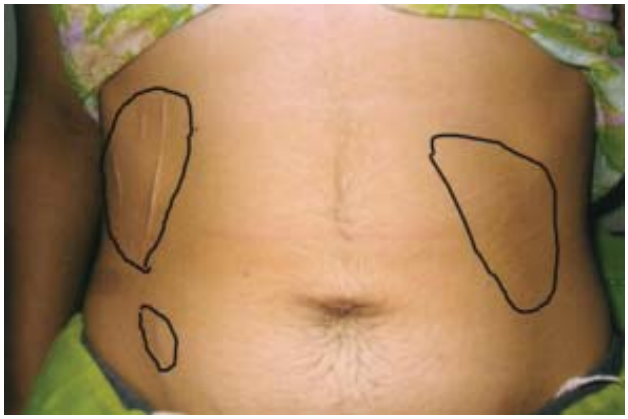

Fig. 1b:

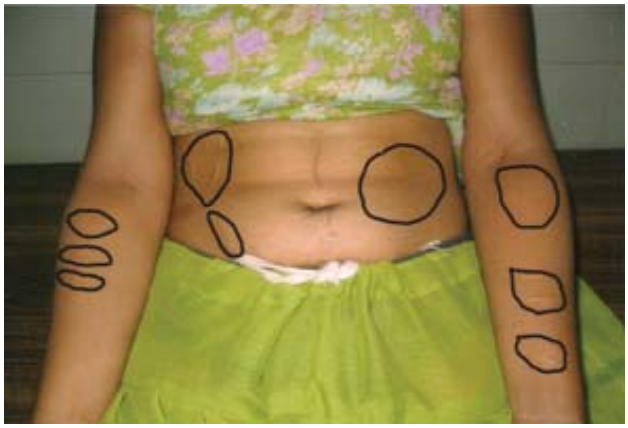

Fig. 1c:

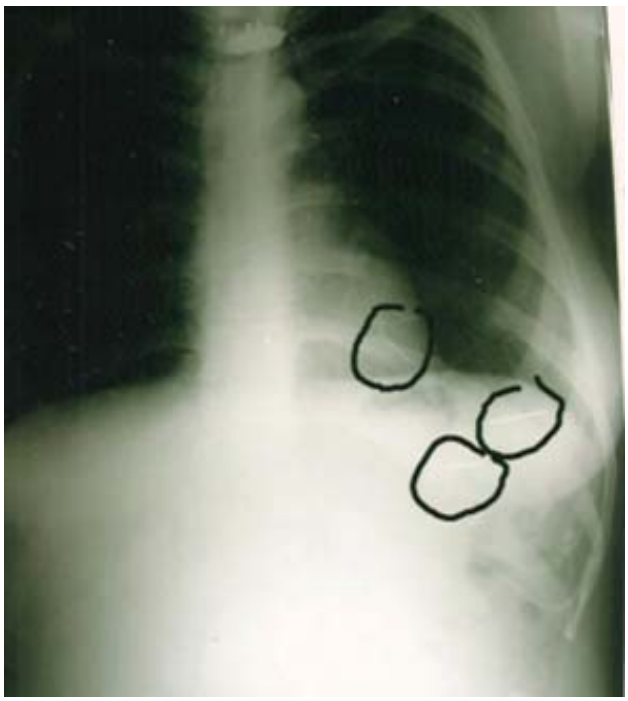

Fig. 2a:

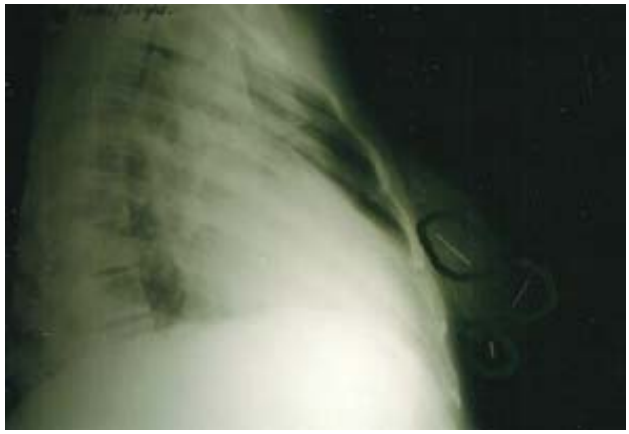

Fig. 2b:

Fig. 3a:

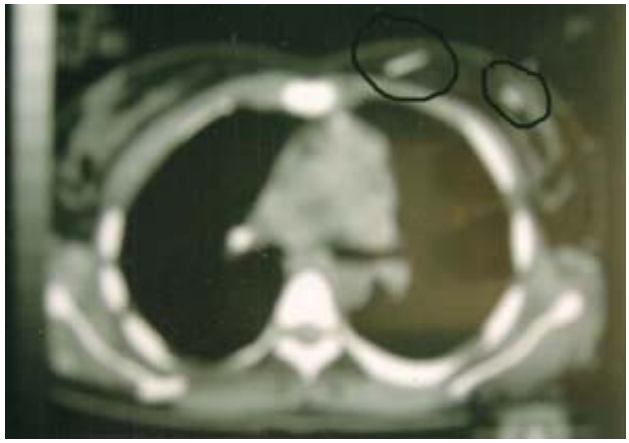

Fig. 3b:

relations with her husband and her husband used to ignore her. There was no history of any type of psychiatric ailment in her family. Now she wanted her pins to be removed. The patient was referred to our hospital psychiatrist and general surgeon for further management.

Discussion

Munchausen's syndrome is a factitious disorder in which those affected feign disease, illness, or psychological trauma in order to draw attention or sympathy. It is a repetitious pattern of medical attention seeking behaviour in which the individual has dramatic but untruthful complaints. The person creates the symptoms of illness and intentionally fakes disease. There are self-induced symptoms or false physical and laboratory findings for the purpose of deceiving clinicians or other hospital personnel. Generally there are three varieties: abdominal type, bleeding type, and those who specialise in faints/fits/palsies. The most common signs and symptoms are chronic diarrhoea, fever of unknown origin, intestinal bleeding or haematuria, seizures or hypoglycaemia, self mutilation. Symptoms and several scars on the abdomen are out of proportion to the physical signs. The sole purpose of faking the disease is to obtain medical attention. There is no other recognisable motive and hence it is different from malingering. In a factitious disorder, the motivation is a psychological need to assume the sick role, as evidenced by an absence of external incentives for the behaviour. In contrast, in malingering the individual has a goal that is obviously recognisable when the environmental circumstances are known.

This particular patient had a very atypical and rare way of creating the disease by inserting pins through the skin on her left breast. This is an unexpected way of faking the illness as compared to the routine mentioned signs and symptoms. These pins were detected by X-ray and CT scan. Such type of patients can create a lot of problems in reaching the final diagnosis.

These are real challenging type of patients and can cause significant social and medical costs. This syndrome should be kept a possibility in the differential diagnosis. The prognosis is usually poor and treatment often unsuccessful. Certain points must be kept in mind by the physician/surgeon after the diagnosis has been made:

1. Avoid the feelings of anger, hostility, and ridicule which are aroused by the discovery of factitious illness.
2. Patient should not be confronted or labelled as a liar. Instead, a psychiatric consultation should be sought.
3. Unnecessary surgical procedures should not be carried-out.

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Starting from this issue, we are incorporating a new column 'Annotations' – either by the editor, or an invited author – primarily to make the journal more enjoyable as well as thought provoking. In the bargain, if we open a route to pass on prescient wisdom, so be it. The idea, basically, is to demystify medical scientific jargon to make the reader start thinking. If the latter purpose is served, we will have made a new beginning. Letters to the editor, on the 'Annotations', are welcome.

There is a precedent for this in the history of medical journalism. George Burch, the celebrated editor of the *American Heart Journal* for four decades, used to write an 'Annotation' in every issue on any thought that occurred to him. It was more on the lines of O. Henry's poem: "Time" he wrote "has come to talk of many things – of Cabbages and Kings". Your editor thinks that the time has come to innovate to progress, by looking back!

– Editor.

"Though we are not now at that strength which in better days moved earth and heaven,
that which we are, we are;
one equal temper of heroic hearts made weak by time and fate but not in will;
To strive, to seek, to find, and not to yield."

– Lord Alfred Tennyson.

Let the Human Mind Loose; Let Science not Bind it!

BM Hegde*

"Intellectual integrity made it quite impossible for me to accept the myths and dogmas of even very great scientists, more particularly of the belligerent and so-called advanced nations. Indeed, those intellectuals who accepted them were abdicating their functions for the joy of feeling themselves at one with the herd."

– Bertrand Russell (1872-1969).

Blinded by the reductionist science of modern medicine, scientists, practising doctors, as also the greedy pharmaceutical industry were after the poor microbes ever since the 1800s trying to win the battle against germs using drugs, vaccines, and even good hygienic methods based on antiseptics of all kinds. The results are there for all to see. We have been successful in creating some really deadly germs by our misplaced faith in antibiotics and other pharmaceuticals. These super bugs have been the cause of many hospital based (nosocomial) infections especially in the old elderly getting admitted to the intensive care units. So much so, lately, intensive care units for the old elderly have become the highways to heaven – known as hospitalism in the 18th Century!

In the year 2000, the Nobel Laureate Joshua Lederberg, writing in the journal *Science,* opined that we should get off the moral high horse and stop calling "germs evil and we good". He wrote that each host and its parasite (man and germ) possibly forge a new super-organism with their genomes merging with one another, yoked as a chimera. Ever since, workers like Steven Gill at the University of Buffalo, Jeffrey Gordon and Herbert Virgin of Washington University School of Medicine in St. Louis, and Sarkis Mazmanian of California Institute of Technology have all come up with evidence that there are many, many such chimeras inside the human system that our human genome, about which we make a lot of noise in reductionist science, is only a small minority of our true genome with thousands of genes incorporated into our cells over the millions of years that we have evolved from a single cell organism. Our present genome, if it could ever be fully understood, can be called the

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meta-genome. In addition, of course, humans have vital genes out-with the nuclear genes that we know of. Douglas C Wallace, in his epoch making article in the journal *Genetics,* has demonstrated these mitochondrial genes using his new MITCHIP. The mitochondrial genes do most of our work.

Do not panic to know that nine out of ten of your body cells are microbial and not yours! This should make all arrogant men and women humble to know that they need the help of so many germs even to survive. It should teach us the great lesson of the Upanishads and, the basis of our educational system, that humility is the greatest virtue. The new science of holism has proved the ancient Indian wisdom to be true. True humility will make this world tranquil without the need for nuclear weapons with all their dangerous fallouts like Chernobyl or Fukushima. In the gut alone, more than 1,000 species of germs bring 100 times more genes than our own body's cell DNA carries. Microbial genes control the energy that we absorb from our food and also how our immune system functions. Now I would let the reader think for a minute about the wisdom of injecting more than 20 vaccines to the innocent bodies of our newborn children in the fond hope of protecting them against diseases from germs. In the new setting of our meta-genome this could even lead to a wrong trigger of the immune system leading to the so-called unknown aetiology "auto-immune diseases." This is only my speculation for the time being. It is very hard to think of our own body cells producing antibodies against our own other body cells as feared by Paul Ehrlich in his "horror autotoxicus" theory. In reality, in the new science of holism, each of our body cells loves all other body cells, as demonstrated by Albert-Fritz Popp's bio-photon camera. It is time to free the mind from the shackles of reductionist science of modern medicine today.

These ideas of microbiomes and viromes (meta-genomes with germs and viruses) would have been thought of as madness by our reductionist pundits who get millions of dollars of grants for genetic engineering and stem cell research. If one patient with blindness could see with the help of stem cell therapy it is highlighted in the newspapers as a great discovery while thousands of failures of the same are never reported. Same is true of genetic engineering of today where the large majority does not help the patient; might even produce another new disease. But the hard nuts keep on doing the same reductionist research not knowing that the millions of germ genomes incorporated into us are having a hearty laugh at our foolishness. Reminds me of what Shakespeare wrote about human pride.

"Man, proud man, dres't in a little brief authority, most ignorant of what he's most assur'd, glassy essence, like an angry ape, plays such fantastic tricks before high heaven, as make the angels weep."

– William Shakespeare (1450-1599).

Every medical student, who enters the portals of our medical schools, nay any professional school, should have a few classes on the art of thinking. The latter was suppressed on day one at kindergarten school where the child is told what to do and what to study! Every child before going to school is the best scientist with a clean slate of a mind and curiosity to know. This natural tendency is curbed at school. In fact, up until 1999, microbiologists had no clue that they were missing millions of species of germs. The enormous undercounting of the species came to light with David Relman of Stanford University showing many more species from human gum smear cultures. Turning to gut and stool specimens they discovered hundreds of new hitherto unknown species. That was the beginning of the thinking on meta-genomes for man. In addition, we also know something new in another area of germ and man relationship which might open another Pandora's box in the near future. In 1934, a German scientist named Emmy Klieneberger-Nobel discovered that the bacteria in her Petri dish had changed form and lost their cell walls in the process. Seventy years later, biomedical researcher Trevor Marshall created a model describing how these bacteria, along with intracellular bacteria and pathogens that live together inside protected communities called biofilms, might be able to cause chronic disease and dysregulate the immune system." (http://bacteriality.com/about-2).

I foresee a new age of enlightenment in medicine with a better understanding of man. Time has come to write on Man, the Known! Next time round, when you see a doctor for a minor illness – syndromes like common cold, feverish cold, sore throat and/or 'flu like illness – do not ask for antibiotic cover. When your doctor wants to prescribe an antibiotic please ask him if that is absolutely necessary in view of the new knowledge of germs and human relationships. Do not believe in antiseptic soaps. They are bad. Simple soap and water is good enough for any kind of washing.

"Where the mind is without fear
and the head is held high; where knowledge is free…
Into that heaven of freedom, my Father,
let my country *(medical world)* ***awake."***

– Rabindranath Tagore.

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