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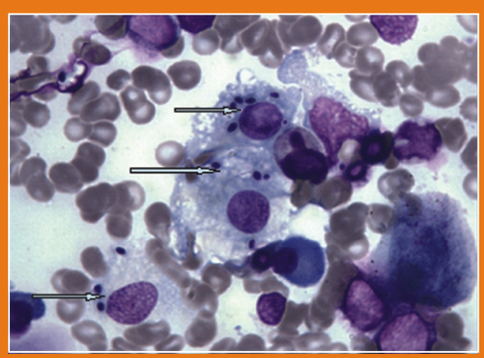

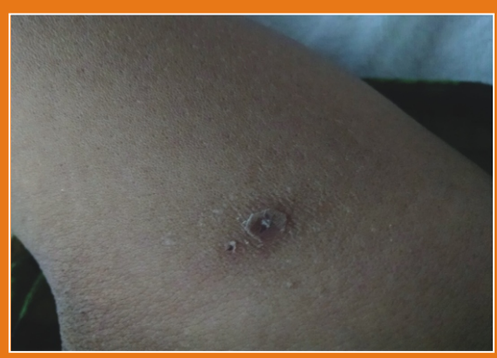

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Contains 80 pages from 73 to 152 (inclusive of all advertisements)

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Journal, Indian Academy of Clinical Medicine • Vol. 18, Number 2, April-June, 2017

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Corrigendum

A mail has been recived from Dr.Vishwas Gulati, the first author of Original Article – "Prevalence of Peripherel Neuropathy in India Prediabetes Subjects and its correlation with Metabolic Risk Factores" published in JIACM, Vol. 17, No. 4, October-December, 2016, stating that names Dr Manish Kumar (Associate Professor, Department of Medicine, PGIMER), and Dr KS Anand, (Professor and Head of the Department of Neurology, PGIMER, Dr Ram Manohar Lohia Hospital) had been omitted inadvertently, and may be included in the list of authors. The needful has now been done.

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VIEWPOINT

JIACM 2017; 18(2): 78-79

Can We Comprehend Much More Than We Can Grasp?

*BM Hegde**

Science should try and understand Nature. That is the main purpose of science. Technology, on the other hand is for making money. It has brought lots of personal comforts to mankind. Therefore, it is venerated by all. Unfortunately, technology is pushing science beyond its calling of understanding nature to trying to teach nature a lesson or two to get the industry make a faster buck! In the bargain, many scientists are being pushed to make science bend to the wishes of the vested interests, engineered by the greedy industry, unbeknownst to the scientists. A few scientists also join hands with the industry in their clandestine designs. This today is the bane of science. Basic science has changed a lot and has almost come closer to spirituality and eastern philosophy but the technocrats are resisting that wisdom to come to common knowledge.

Our dilemma today is due to the confusion of having the 19th century science, 20th century technology, and 21st century wisdom to grapple with. Western science minus quantum physics is dead science. This is glaring in biology. The new evolutionary biology has thrown new light on evolution sans the time honoured Darwin-Mendel conundrum. This world which has been in existence for four billion years had the first two billion with germs running the show all by themselves. They even made their initial mistakes and learnt their lessons. They then mutated to live in harmony and invented chlorophyll for energy. They further went in for compassion by donating their individual DNAs to form the first nucleated cell. Does not this sound like Indian philosophy of "paropakaararthamidamshareeram?" (we live for others) That nucleated cell (zygote) is our origin. Human biology (physiology) is a closed system in systems biology. The zygote goes on dividing to make eventually what you and I are. We are not organs separately put together to make a whole. It is the whole which has divided to become a bigger whole. Therefore, we have a large baggage of our ancestors, the germs, with us. In fact, we are outnumbered by them 1:10. Finally, human body is a happy colony of 120 trillion human cells and ten times that number of germ cells.

Energy being the same as matter, the human body becomes an illusion of the human mind. It is natural that one cannot touch or feel the mind but you can make out its effects. It is the consciousness which has no particle shape but has only a wave existence and is found all over the body and outside of it also. It is in fact the canvas on which our emotions and thoughts are flashed. The human body can change from particle to wave and back almost 1,024 (Planck's constant) times in a second. Just as an atom has the blueprint of a molecule in it, the human wave form has the blueprint of its particle form as well. In short, all living things are interconnected – not just human beings alone. This can be made use of in quantum healing where self-healing is achieved by making the wave forms to change the particle form as and when needed. We have the power to heal ourselves in the unlikely event of our falling ill.

This was my research interest for the last five years and I am happy to present results. I have not yet started using this method on willing patients with their informed consent. At times, I try it on myself. I did not regret it so far. Theoretically anything from common cold to cancer could be helped, but this needs the active participation of the patient in a tranquil state of mind, say meditation. Since this world is incredibly interactive and coherent at all levels, it is unlikely that the individual consciousness units are distinct from the universal consciousness. Consciousness is a fundamental part of all existence. David Bohm and others have clearly shown that in physics and mathematics there is good evidence for a deeper organising and informing wave function. As Hans Peter Duerr put it "matter is not made out of matter" but only of energy.

Unfortunately, western medicine is still neck deep in Newtonian 19th century physics of deterministic predictability. That is where we are able to comprehend only what we see or feel but not what we do not see. Our five senses are the only source of our information. Out there is this vast sea of quantum wisdom that cannot be grasped using the linear mathematics of Newtonian physics. Our medical training has not changed, while science has changed completely since 1925 when Werner Heisenberg propounded the Uncertainty principle. 21st century is the century of new biology where consciousness rules the roost. All matter is derived from consciousness.

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

Today we can comprehend much more than what we can grasp with our five senses. Let us make use of that new knowledge to help the suffering humanity. That will, of course, change the course of modern medical practice. The medical technocrats and the trillion dollar drug lobby may not be so upbeat about this new found wisdom in medicine as it does not bring them greater joy materially. Materialistic science of medicine should give place to the new Reality. The caption of this paper is taken from one of Hans Peter's writings in quantum physics.

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"Good lies beyond thought, like beauty.
Where good is, there is order – not the order of authority, punishment and reward...
The law of the good is everlasting, unchanging and timeless.
Stability is its nature and so it is utterly secure."

– J. KRISHNAMURTI.

ORIGINAL ARTICLE

JIACM 2017; 18(2): 80-83

Assessment of Right Ventricular Systolic Dysfunction in Patients of Dilated Cardiomyopathy with The Help of Tricuspid Annular Plane Systolic Excursion and its Correlation with New York Heart Association Classification of Congestive Heart Failure

M Chaturvedi, SK Prajapati**, Balvir Singh*, Suryakamal Verma***

Abstract

Introduction: *Dilated cardiomyopathy is an important cause of heart failure. In terminal stage of DCMP, RV systolic dysfunction is an important independent predictor of long-term mortality. In the present study we assessed RV systolic dysfunction in DCMP patients with help of TAPSE and correlated it with NYHA class of CHF to predict mortality.*

Aims and objective: *Assessment of RV systolic dysfunction in patients of DCMP with the help of TAPSE and its correlation with NYHA classification of CHF. The end-points studied were: (1) RV systolic dysfunction assessment by use of TAPSE; (2) Correlation of TAPSE with NYHA classification of CHF. (3) To establish TAPSE as an objective measure to assess severity of HF in DCMP patients.*

Methodology: *This study was conducted in SN Medical College, and 150 patients of DCMP were confirmed on the basis of ECHO criteria such as LVEF < 45%, LVEDd > 3 cm/body surface area, Global hyokinesia and dilatation of all the chambers of heart. We excluded patients of other cardiovascular disorders from our study. We assessed RV systolic dysfunction by measuring TAPSE, classified patients in 4 classes according to NYHA classification of CHF, then we calculated mean of TAPSE for each class and recognised correlation between these two with the help of 't test', p value of this test was <0.0001.*

Results: *In our study RV systolic dysfunction was 0%, 25%, 33.33%, and 90.91% in NYHA class I, II, III and IV respectively. In NYHA class II and III patients, only mild RV systolic dysfunction was present, whereas in NYHA class IV mild, moderate and severe RV systolic dysfunction was present. Our study found that for higher NYHA class, TAPSE value was lower.*

Conclusion: *Higher NYHA class of heart failure in patients of DCMP correlated well with lower TAPSE and TAPSE can be used as an objective measure in patients of DCMP to assess severity of heart failure as there is inverse relationship between TAPSE and NYHA class of heart failure.*

Keywords: *DCMP, RV systolic dysfunction, TAPSE, NYHA, CHF.*

Introduction

Dilated cardiomyopathy (DCMP) is an important cause of heart failure and accounts for up to 25% of all cases of Congestive heart mailure (CHF) in daily clinical practice[1]. Progression of DCMP is routinely predicted by time honoured NYHA classification of CHF. As the New York Heart Association (NYHA) grade increases, annual mortality rate increases. In the terminal stage of DCMP, Right Ventricle (RV) systolic dysfunction is an important independent predictor of long-term mortality. LV systolic dysfunction (LVEF) is routinely used to assess long-term mortality, but RV is not commonly assessed due to triangular shape, complex geometry and incomplete visualisation of RV in standard apical four chamber view.

With advancement of echocardiography, various criteria for assessment of RV systolic dysfunction like RIMP, TAPSE, FAC, 2D RVEF and S0 are developed[2]. Out of them Tricuspid Annular plane systolic excursion (TAPSE) is commonly used in clinical setting. TAPSE or Tricuspid annular motion (TAM) is a method to measure the distance of systolic excursion of the RV annular segment along its longitudinal plane, from a standard apical 4-chamber window. In the present study, we have attempted to predict mortality in patients of DCMP by assessment of RV systolic dysfunction with help of TAPSE and then correlating it with NYHA class of CHF.

Material and methods

The data for this study were obtained from the Cepartments of Cardiology and Medicine at SN Medical College, Agra, Uttar Pradesh (INDIA). A total of 150 patients fulfilling the inclusion criteria from March 2014 to June 2015 were recruited.

We selected patients of DCMP, diagnosed on the basis of symptoms and signs of heart failure and ECHO criteria such as LVEF < 45%, LVEDd > 3 cm/body surface area, global

**Professor, **Junior Resident, Department of Medicine, Sarojini Naidu Medical College, Agra - 282 002, Uttar Pradesh.*

hyokinesia/RWMA and dilatation of all chambers of the heart. We excluded patients of valvular heart disease, congenital heart disease, pericardial disease, cor-pulmonale with CHF, hypertrophic cardiomyopathy, restrictive cardiomyopathy and systemic hypertension from the study.

All patients included in the study underwent a thorough clinical evaluation of symptoms and signs of heart failure and routine blood investigations, echocardiography, chest radiography and electrocardiography were done to collect data. We assessed RV systolic dysfunction by measuring TAPSE and classified patients according to NYHA classification of CHF. We then calculated mean of TAPSE for each class and recognised correlation between these two with the help of 't test', p value of this test was <0.0001.

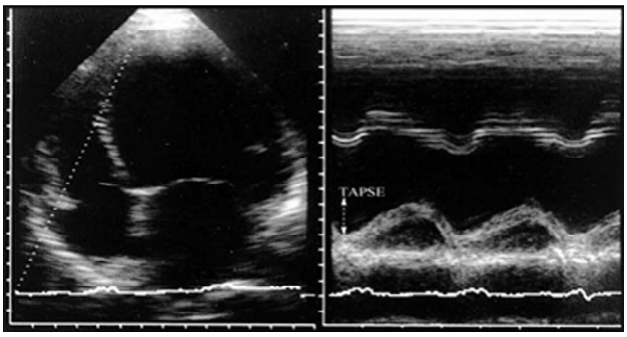
In Fig. 1, M-mode cursor is positioned at the lateral portion of the tricuspid annulus in apical four chamber view. And in Fig. 2, M-mode recording of the TAPSE, from the same approach, is shown.

We took values of TAPSE of 16 - 20 mm, 11 - 15 mm, 6 - 10 mm and 5 mm or less for normal, mild, moderate and severe RV systolic dysfunction, respectively. (As per British Society of Echocardiography education committee).

Observations

As shown in Table I, in our study out of 150 patients, 56% patients had RV systolic dysfunction on the basis of TAPSE. Among these patients, RV systolic dysfunction was 0% in NYHA class I , 25% in NYHA class II, 33.33% in NYHA class III and 90.91% in NYHA class IV. In NYHA class II, III patients, only mild RV systolic dysfunction was present, whereas in NYHA class IV mild, moderate and severe RV systolic dysfunction was present in 45.45%,36.36 and 9.09% cases, respectively.

Overall, 44% patients had normal RV systolic function, 36% patients (54 cases) had mild RV systolic dysfunction, 16%



Figs. 1 and 2:

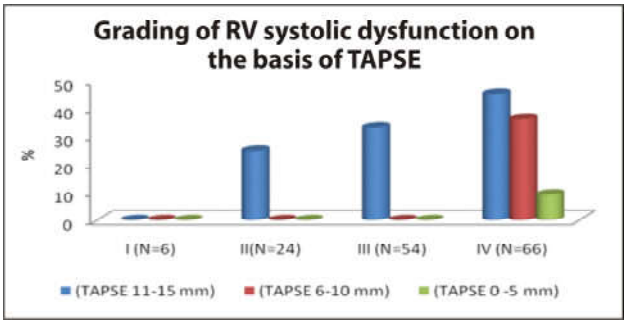


Fig. 3: *Prevalence and grading of RV systolic dysfunction on the basis of TAPSE in patients of DCMP.*

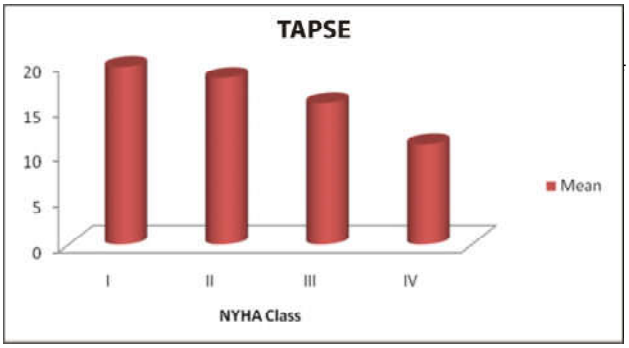


Fig. 4: *Correlation of TAPSE with NYHA class of heart failure in patients of DCMP.*

Table I: Prevelence and grading of RV systolic dysfunction, on the basis of TAPSE, in patients of DCMP.

S. No.	NYHA class of HF (No. of cases in each class)	RV systolic dysfunction		Mild RV systolic dysfunction (TAPSE 11 - 15 mm)		Moderate RV systolic dysfunction (TAPSE 6 - 10 mm)		Severe RV systolic dysfunction (TAPSE 0 - 5 mm)	
		No.	%	No.	%	No.	%	No.	%
1.	I (N = 6)	0	0	-	-	-	-	-	-
2.	II (N = 24)	6	25	6	25.00	-	-	-	-
3.	III (N = 54)	18	33.33	18	33.33	-	-	-	-
4.	IV (N = 66)	60	90.91	30	45.45	24	36.36	6	9.09
	Total (N = 150)	84	56	54	36	24	16	6	4

patients (24 cases) had moderate RV systolic dysfunction and 4% patients (6 cases) had severe RV systolic dysfunction.

Table II: Correlation of TAPSE with NYHA class of heart failure in patients of DCMP.

NYHA Class	No. of patients	TAPSE (mm)		P value
		Mean	SD	
I	6	19.67	1.21	<0.0001
II	24	18.50	2.34	<0.0001
III	54	15.67	2.65	<0.0001
IV	66	11.09	3.17	<0.0001

As shown in Table II, we correlated values of TAPSE with NYHA classification of heart failure in patients of DCMP. Our study showed that in NYHA class IV, mean TAPSE value was 11.09 ± 3.17 mm, in NYHA class III, mean TAPSE value was 15.67 ± 2.65 mm, in NYHA class II, mean TAPSE value was 18.50 ± 2.34 mm, and in NYHA class I, mean TAPSE value was 19.67 ± 1.21 mm.

We applied 't' test to check for correlation of TAPSE with NYHA class of heart failure.The mean values of TAPSE obtained in each NYHA class were statically significant. P values obtained were <0.0001.

Bar diagram in Fig. 3 shows correlation of TAPSE with NYHA class of heart failure in patients of DCMP.

Discussion

TAPSE as a measure of RV ejection fraction was first proposed by Kaul *et al* in 1984, who demonstrated a close correlation to RV ejection fraction determined by radionuclide technique[3]. This has been confirmed in subsequent studies in patients with HF or ischaemic heart disease using thermo-dilution techniques or Magnetic Resonance Imaging[4]. TAPSE may be related to RVEF, because the RV free wall consists predominantly of longitudinal and oblique myocardial fibres and because the RV sinus is the major contributor to the combined RV stroke volume[5]. The present study is a large scale study to evaluate RV systolic dysfunction with the help of TAPSE in patients of DCMP presenting with new onset/worsening heart failure and to correlate TAPSE values with NYHA class of heart failure. TAPSE has been used as an indicator of RV systolic function in various studies. Lee CY *et al* (2007) concluded that the frequency of rehospitalisation was inversely correlated with RVEF and!TAPSE!in SSc patients[6]. This study found a positive correlation between RVEF and TAPSE. Tamborini G *et al* (2007) concluded that FSA, TAPSE, PSV are important parameters in evaluation of RV systolic function and significantly associated with prognosis. Lower values of these parameters are associated with impaired RV systolic function[7].

In our study, all patients had normal RV systolic function in class I NYHA, 25% (6 cases) had RV systolic dysfunction in class II NYHA, 33.33% (18 cases) patients had RV systolic dysfunction in class NYHA III, 90.91% (60 cases) patients had RV systolic dysfunction in NYHA class IV. These data show that with increasing grade of NYHA class, frequency of RV systolic dysfunction also increased.

We correlated values of TAPSE with NYHA classification of heart failure in patients of DCMP. Our study shows that in NYHA class IV mean TAPSE value was 11.09 ± 3.17 mm, in NYHA class III mean TAPSE value was 15.67 ± 2.65 mm, in NYHA class II mean TAPSE value was 18.50 ± 2.34 mm, and in NYHA class I mean TAPSE value was 19.67 ± 1.21 mm. We took p value <0.0001. Similar results were obtained from various other studies. Ereminiene E *et al* (2012) studied 119 patients with non-ischemic DCMP and ischemic heart disease and found that in patients with different LV dysfunction severity the higher NYHA class correlated with lower TAPSE dimensions: NYHA class IV 12.7 +/- 2.9 mm vs NYHA class III 15.9 +/- 4.2 mm and NYHA class II 18.8 +/- 4.2 mm, P < 0.001[8]. Ghio S *et al* (2000) studied 140 consecutive patients with chronic CHF and a left ventricular ejection fraction <35%. TAPSE < or =14 mm added significant (p <0.03) prognostic information to NYHA class III or IV, left ventricular ejection fraction of <20%, and mitral deceleration time of < 125 ms[9]. These studies found similar inverse correlation of TAPSE with NYHA class of heart failure.

Our study concluded that lower TAPSE values were associated with higher NYHA class. As higher NYHA class is an indicator of adverse prognosis in patients of DCMP, our study indirectly recognised adverse prognosis with lower TAPSE values in DCMP patients. Almost similar inference is drawn from various studies suggesting TAPSE as an adverse prognostic indicator in various diseases. JesperKjaergaard *et al* (2007) studied 817 patients and concluded that decreased TAPSE as well as presence of COPD were independently associated with adverse short- and long-term survival[10]. Saurabh Gupta *et al* (2008) studied 25 patients and concluded TAPSE as an important parameter among all RV echocardiographic parameters for prognosis[11]. MokotoAmaki *et al* (2012) studied 30 patients and concluded that unmasked right ventricular dysfunction may explain functional capacity in patients with heart failure, and may be linked to prognosis[12].

Conclusion

Our study concluded that higher NYHA class of heart failure in patients of DCMP is correlated well with lower TAPSE dimension. As both right ventricular systolic dysfunction and NYHA class of heart failure have prognostic importance,

it is easy to assess the prognosis of patients with the help of TAPSE, because of inverse relationship between TAPSE and NYHA class of heart failure. As calculation of TAPSE dimension with the help of M mode echocardiography is convenient and easy, TAPSE dimension of DCMP patients is very helpful for predicting the prognosis of patients. Findings of our study are supported by almost similar results obtained by several other studies in the past.

With this study we can say that TAPSE can be used as an objective measure in patients of DCMP to assess severity of heart failure as there is inverse relationship between TAPSE and NYHA class of heart failure. It is strongly recommended that TAPSE should be incorporated into the routine echocardiographic examination and report, and this is particularly important when RV dysfunction is suspected such as in DCMP and or when the clinical indication for the study relates to a condition that may affect the right ventricle.

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"Rebellion has nothing to do with the crowd, politics, power, or violence.
Rebellion is individual;
it has something to do with changing your consciousness, your silence, your being.
It is a spiritual metamorphosis."

– OSHO.

ORIGINAL ARTICLE

JIACM 2017; 18(2): 84-90

Parathyroid Hormone Status and Vascular Calcification Determined by Abdominal Aortic Calcification (AAC) Score in Patients of Chronic Kidney Disease Stage 4 - 5 and their Correlation with Various Risk Factors

Nitya Nand, Nisha Batra**, Virender Chauhan**, Manoj Yadav***

Abstract

Introduction: *Disturbances in bone and mineral metabolism are an important cause of morbidity and mortality in chronic kidney disease (CKD) patients. The prevalence of adynamic bone disease (ABD) associated with hypoparathyroidism has recently increased and is found to be associated with vascular calcification and increased cardiovascular mortality. Risk factors of hypoparathyroidism have been found in some studies but the aetiology is yet to be known. The aim of this study was to evaluate, in patients of CKD stage 4 - 5, the parathyroid hormone status and prevalence of vascular calcification (abdominal aortic) and to evaluate their association with various risk factors.*

Methods: *50 patients (Group A) on medical treatment and 50 patients (Group B) undergoing regular haemodialysis were included in the study. Patients were investigated for serum intact parathyroid hormone (iPTH) levels and classified as euparathyroid, hyperparathyroid and hypoparathyroid as per the target recommendation of iPTH levels by KDOQI. Multiple risk factors were compared in these subgroups to evaluate their possible association with PTH status. X-ray of lumbar spine was done in all patients to look for the abdominal aortic calcification (AAC) and a score was calculated (AAC Score) which was correlated with parathyroid status and various other risk factors.*

Results: *Mean age of the study group was 51.37 ± 16.16 years. Overall 34% patients were found to be hypoparathyroid while 38% patients were hyperparathyroid. Group B had maximum hypoparathyroid patients (46%) while group A had maximum hyperparathyroid patients (44%) and least hypoparathyroid patients (22%) and this difference was significant. Other factors found to be significantly associated with low iPTH levels were increasing age, diabetes mellitus and higher serum calcium levels. 59% of the patients had evidence of abdominal aortic calcification with mean AAC score of the whole study group as 2.04 ± 2.47.*

Conclusion: *There is high prevalence of relative hypoparathyroidism and vascular calcification in CKD patients. Factors correlated with low iPTH levels were age, diabetes mellitus, haemodialysis and higher serum calcium levels but the factors predictive of AAC were age and probably the parathyroid status.*

Keywords: *Abdominal aortic calcification (AAC), CKD-MBD, vascular calcification, hypoparathyroidism.*

Introduction

CKD-mineral bone disorder (CKD-MBD) is an area of ongoing discussion as it is an important cause of morbidity and mortality in CKD patients. The biochemical markers used in evaluation of bone remodelling include serum parathyroid hormone (PTH) calcium, phosphorus and alkaline phosphatase levels. Earlier, osteitis fibrosa cystica used to be the predominant lesion. The prevalence of adynamic bone disease (ABD) associated with hypoparathyroidism has recently increased. This is reported to be as high as 64.4% among haemodialysis patients[1] and is found to increase the risk of fractures and vascular calcification and hence cardiovascular mortality[2] in CKD patients. Risk factors of hypoparathyroidism have been studied but the aetiology is yet to be proven. Asian dialysis patients could be at higher risk of hypoparathyroidism due to their ethnicity, as it is a common observation from countries like Japan and Taiwan[4]. Cardiovascular disease is the leading cause of mortality in CKD patients. One potential mechanism by which this occurs is through vascular calcification. Electron Beam CT (EBCT) is the standard technique to measure the arterial calcification; however, it is very expensive and not available everywhere. Abdominal aortic calcification determined by Lateral Lumbar radiographs can be used as an indirect measure of arterial calcification and studies show the abdominal aortic calcific deposits to be equally predictive of cardiovascular disease and mortality[5]. Pathogenesis of vascular calcification in CKD is multifactorial and is due to both traditional and uraemia-specific risk factors including disorders of bone and mineral metabolism. However, the associations do not prove causality and prospective studies are needed to confirm the role of various factors. Since there are considerable variations among different studies and most of these studies have been done in western population, Indian data is scarce in

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this regard. Hence the present study was done to evaluate the parathyroid status and vascular calcification as determined by abdominal aortic calcification (AAC) score in Indian CKD patients of stage 4 - 5.

Material and methods

A total of 100 patients of CKD stage 4 and 5 were included in the study. They were divided in two groups, group A comprised of fifty patients undergoing conservative management with medical treatment and group B included fifty patients on regular haemodialysis in addition to the medical treatment. Patients undergoing regular haemodialysis for at least one month were included in group B. Those with history of primary parathyroid disease; or parathyroidectomised; or using steroids and immunosuppressive drugs were excluded from the study. A pre-informed consent was obtained from every case before inclusion in the study.The clinical and demographic profile was recorded in a specially designed performa. All the patients were investigated for serum intact parathyroid hormone (iPTH) levels using chemiluminescense immune assay (CLIA) method and were further classified as euparathyroid, hyperparathyroid and hypoparathyroid as per the target recommendation of iPTH levels by KDOQI according to which euparathyroid status is defined as serum iPTH levels of 70 - 110 pg/ml in stage 4 and 150 - 300 pg/ml in stage 5 with any value below or above this range as hypoparathyroid and hyperparathyroid, respectively.

X-ray lateral view of lumbar spine was done in all patients to look for abdominal aortic calcification (AAC) and a score was calculated (AAC Score) using the following:–

Calcification of anterior and posterior wall of the aorta at the level of L1 to L4 vertebra was noted and scored from 0 - 3. Scoring was given as: 0 for no calcification; 1 for calcification of less than 1/3rd of the length of that lumbar segment; 2 for calcification of 1/3rd to 2/3rd length; and 3 for calcification of more than 2/3rd length of the aortic wall of that lumbar segment. Scores of anterior and posterior aortic wall of all 4 lumbar segments were added up together to calculate the final AAC score which ranged between 0 - 24. Based on the score, patients were categorised in 3 subgroups – no calcification for AAC score 0; mild calcification for AAC score 1 - 6; and significant calcification for AAC score 7 - 24.

Multiple risk factors were compared in these subgroups to evaluate their possible association with PTH status as well as AAC score.The factors included – age and sex, aetiology of CKD, CKD duration, management group (Conservative vs. Haemodialysis group), haemodialysis duration, blood pressure, renal function tests, proteinuria and serum albumin levels, serum lipid profile and CKD-MBD parameters including serum corrected calcium and inorganic phosphate levels, calcium phosphate product and serum alkaline phosphatase.

Statistical analysis: All the statistical comparisons were done with Graph Pad Instat Version 3.0 software and p values were obtained. Continuous variables were compared between two groups (group A versus group B) by 'independent t-test'. Categorical data were compared using Chi-square test. Analysis of variance (ANOVA) was used to compare the quantitative data among 3 or more groups. Tukey-Kramer multiple comparison test was used as a post-test statistical method only when ANOVA showed a significant difference. Linear regression test was used to assess the correlation of AAC score with individual biochemical parameters. Finally, multiple regression analysis was performed with those risk factors that yielded positive results in their individual linear regression test.

Observations

Mean age of the study group was 51.37 ± 16.16 years and the mean age of group A and group B were 54.16 ± 15.94 and 48.58 ± 16.06 years, respectively but the difference was not significant (p = 0.0844). 61 patients in our study were males. Group A consisted of 6 patients in CKD stage 4 and 44 patients in stage 5 while all the 50 patients in group B were stage 5 CKD. Average duration of CKD was 7 months with a wide range of 0 (recently diagnosed) to 48 months. Group A patients had CKD of lesser duration (4.22 ± 8.09 months) as compared to group B (9.86 ± 9.72 months). Group A patients had significantly higher weight, serum cholesterol levels, serum protein and albumin levels than group B despite similar levels of 24 hour proteinuria, indicative of less catabolic status in group A while serum creatinine levels were higher and mean GFR was lower in group B (Table I). All other biochemical parameters were similar in 2 groups. Chronic glomerulonephritis (CGN) was found to be the most common cause of CKD followed by diabetic nephropathy in group B, while in group A DM was more common than CGN. No aetiologic cause could be determined in 12 patients (Table I).

Overall, 34% patients were found to be hypoparathyroid while 38% patients were hyperparathyroid and only 28% patients had normal parathyroid status according to their CKD stage. Mean serum iPTH levels in group A (297.21 ± 198.90) were more than group B (233.05 ± 208.46). Although this difference was not significant (p = 0.1071); but group A had maximum hyperparathyroid patients (44%) and group B had maximum hypoparathyroid patients (46%) and this difference, when analysed by chi square test, came out to be statistically significant (p = 0.0394). This chi square test also showed a significant linear trend in

the proportions of subgroups in both of the groups (p = 0.0337). Age was found to be a very significant risk factor for hypoparathyroidism. Hypoparathyroid patients were elder (59.18 ± 14.93 years) than euparathyroid (47.71 ± 14.24 years) and hyperparathyroid patients (47.08 ± 16.35 years) and the difference was significant (p = 0.0019). Aetiology of CKD also came out to be a significant risk factor as two-thirds of the diabetic nephropathy patients were hypoparathyroid while only 10% patients of chronic glomerulonephritis (CGN) were hypoparathyroid. Although age was a confounding risk factor because CGN patients were younger than DM patients, other aetiological groups did not show this much hypoparathyroidism, despite being in the same age range as diabetic patients.

Table I: Baseline characteristics of patients in study groups.

	Total (n)	Group A (n)	Group B (n)	P value
Age (mean ± SD)	51.37 ± 16.16	54.16 ± 15.94	48.58 ± 16.06	0.0844
Mean weight (kg)	55 ± 9.72	57.18 ± 9.83	52.86 ± 9.2	0.0255
S. creatinine (mg/dl)	8.47 ± 3.73	7.44±3.96	9.5±3.19	0.0051
Mean corrected Ca (mg/dl)	8.90 ± 1.17	8.77 ± 1.02	9.03 ± 1.31	0.2641
Mean PO4 level (mg/dl)	6.58 ± 1.65	6.48 ± 1.3	6.67 ± 1.95	0.556
Ca X PO4 product (mg^2/dl^2)	58.38± 16.79	56.44 ± 11.48	60.16 ± 20.95	0.2730
S. Alkaline phosphatase (IU/L)	157.07±100.83	156.14±71.78	158±124.05	0.9271
Serum TG (mg/dl)	167.44 ± 76.26	182.78 ± 89.99	152.10 ± 56.31	0.0437
Serum chol (mg/dl)	160.74 ± 44.12	171.74 ± 50.73	149.74 ± 33.34	0.0119
Proteinuria (g/day)	1.562 ± 1.288	1.615 ± 1.539	1.509 ± 0.988	0.6833
Serum protein (g/dl)	6.30 ± 0.79	6.48 ± 0.81	6.12 ± 0.73	0.0235
Serum albumin (g/dl)	3.13 ± 0.45	3.27 ± 0.47	2.99 ± 0.38	0.0011
Hypoparathyroid (n)	34	11	23	0.0394
Euparathyroid (n)	28	17	11	
Hyperparathyroid (n)	38	22	16	
AAC score (mean ± SD)	2.04 ± 2.47	2.28 ± 2.45	1.80 ± 2.45	0.3329 (ANOVA)

Hypoparathyroid patients had a significantly higher mean serum calcium level (9.65 ± 1.11 mg/dl) as compared to euparathyroid (8.85 ± 0.97 mg/dl) and hyperparathyroid (8.26 ± 0.97 mg/dl) patients (p < 0.0001). Six patients in our study had serum calcium levels above the target range and they all were hypoparathyroid. Serum phosphate levels and calcium-phosphate product did not show any significant difference among the 3 groups (p = 0.3353 and 0.3596, respectively) but serum alkaline phosphatase was found to

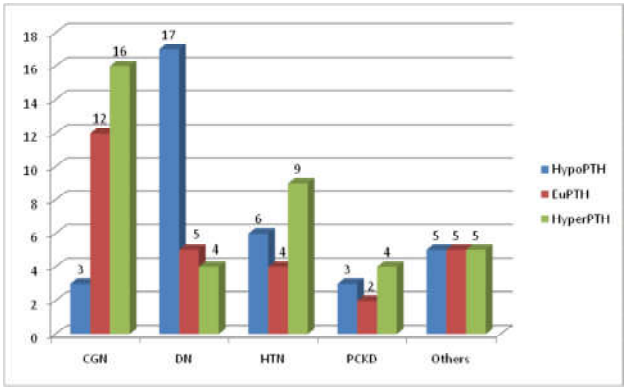

Fig. 1: *Comparison of parathyroid status among various aetiological groups.*

be significantly higher in hyperparathyroid patients (196.42 ± 132.47 IU/L) and lower in hypoparathyroid (117.53 ± 73.49 IU/L) patients as compared to euparathyroid patients (151.68 ± 49.51) with a p value of 0.0031. There was no significant difference between sex ratio, weight, height, BMI and blood pressure values among the 3 groups. Mean haemoglobin levels, levels of uraemic toxins (urea, creatinine, uric acid and potassium), serum albumin levels, 24 hour proteinuria and all 5 parameters of lipid profile of all parathyroid groups were also not found to be significantly different (Table II).

Table II: Comparison of various risk factors among parathyroid groups.

	Hypoparathyroid	Euparathyroid	Hyperparathyroid	P value
Number (n)	34	28	38	
Mean age (years)	59.18 ± 14.93	47.71 ± 14.24	47.08 ± 16.35	0.0019
Corrected S. Ca (mg/dl)	9.65 ± 1.11	8.85 ± 0.97	8.26 ± 0.97	<0.0001
S. iPO4 (mg/dl)	6.22 ± 1.34	6.76 ± 1.89	6.73 ± 1.76	0.3353
CaXPO4 (mg^2/dl^2)	60.45 ± 17.88	59.89 ± 19.44	55.21 ± 13.71	0.3596
S. ALP (IU/l)	117.53 ±73.49	151.68 ± 49.51	196.42 ± 132.47	0.0031
Proteinuria(g/day)	1.93 ± 1.572	1.33 ± 0.704	1.404 ± 1.298	0.1189
S. Albumin (g/dl)	2.99 ± 0.32	3.19 ± 0.43	3.22 ± 0.54	0.0659
CGN (n)	3	12	16	0.0027
DM (n)	17	5	4	0.0004
HTN (n)	6	4	9	0.5487
PCKD (n)	3	2	4	
Others (n)	5	5	5	

Abdominal aortic calcification was found in 59% of our patients, of which 7% had significant aortic calcification (AAC score ≥ 7) (Fig. 2). Mean AAC score of the whole study group was 2.04 ± 2.47. Patients on conservative medical management (group A) as well as haemodialysis (group B)

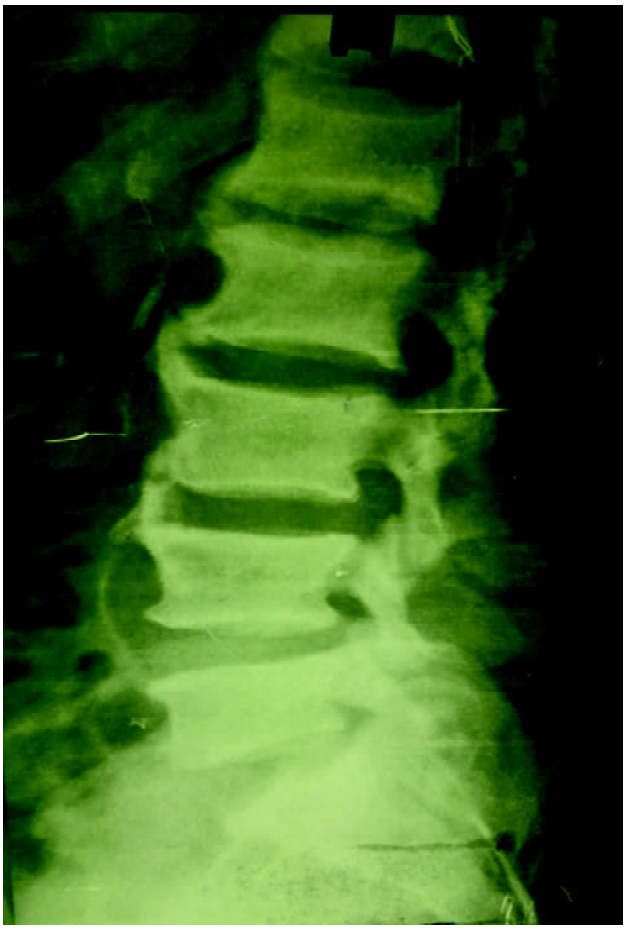

Fig. 2: *Lateral X-ray lumbar spine showing abdominal aortic calcification.*

had similar levels of vascular calcification as the mean AAC score showed insignificant difference between the two groups (p = 0.3329).

Abdominal aortic calcification score, when correlated with age by linear regression test, was found to be highly significant (p < 0.0001) with correlation co-efficient (r = 0.7156) (Fig. 3). Mean AAC score of young (age < 40 year) patients was only 0.20 ± 0.71, while that of middle-aged (age 40 - 59 years) patients was 1.24 ± 1.4 and elderly patients (age ≥ 60 years) was 4.11 ± 2.63 (Table III). This difference was also found to be highly significant (p < 0.0001) by ANOVA. On further analysis, by Tukey-Kramer multiple comparison test, difference between young and middle-aged patients was found to be non-significant while elderly group was found to have significantly greater AAC score (p < 0.001), than the other 2 groups.

Hypoparathyroid, euparathyroid and hyperparathyroid patients did not show any significant difference (p = 0.2404) in their vascular calcification in terms of the mean AAC scores of hypoparathyroid (2.53 ± 2.03), euparathyroid (1.46 ± 2.13) and hyperparathyroid (2.03 ± 2.96). However, Chi

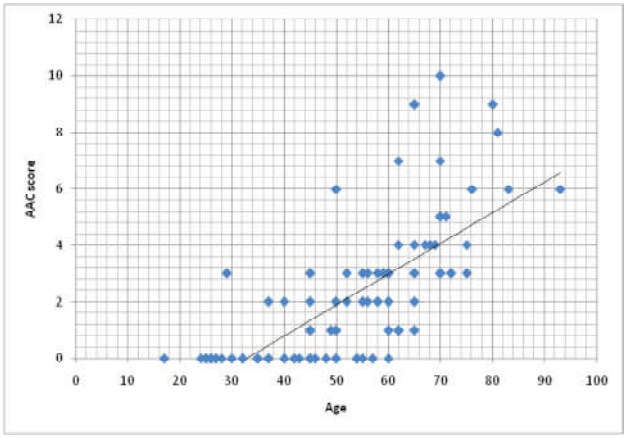

Fig. 3: *Correlation of AAC score with age.*

square test revealed a significantly higher (p = 0.0129) vascular calcification in hypoparathyroid group (26 out of 34) than euparathyroid (15 out of 28) and hyperparathyroid (18 out of 38) patients. Although hypoparathyroid patients showed a higher mean AAC score, most of them had only mild vascular calcification (76%). On the other hand significant vascular calcification was found to be more prevalent in hyperparathyroid group (13%) than other 2 groups (3 - 4%). Overall, mean AAC score of both the hypo and hyperparathyroid groups was more than euparathyroid group (Table IV).

Table III: Correlation of AAC (mean score and severity) with age.

	AAC score (mean ± SD)	No calcification (AAC score 0) (n)	Mild calcification (AAC score 1 - 6) (n)	Significant calcification (AAC score 7 - 24) (n)	P value
Total	2.04 ± 2.47	41	52	7	
Young (<40 year)	0.20 ± 0.71	23	2	0	<0.0001
Middle-age (40 - 59 year)	1.24 ± 1.4	17	21	0	(ANOVA) <0.0001
Elderly (≥ 60 year)	4.11 ± 2.63	1	29	7	(chi square)

Table IV: Correlation of AAC (mean score and severity) with parathyroid status.

	Hypoparathyroid	Euparathyroid	Hyperparathyroid	P value
AAC score (mean ± SD)	2.53 ± 2.03	1.46 ± 2.13	2.03 ± 2.96	0.2404 (ANOVA)
No calcification (n)	8	13	20	0.0129
Mild calcification (n)	25	14	13	
Significant calcification (n)	1	1	5	(chi square)

Aetiology of CKD was the strongest factor associated with vascular calcification as mean AAC score varied drastically from 0.19 for CGN to 4.21 and 3.19 for hypertensive nephropathy and diabetic nephropathy, respectively (Fig. 4). However, age remained as a confounding factor in this analysis as CGN patients were the youngest and the mean AAC score of all 5 aetiological groups were in the same order as their mean age (Fig. 5).

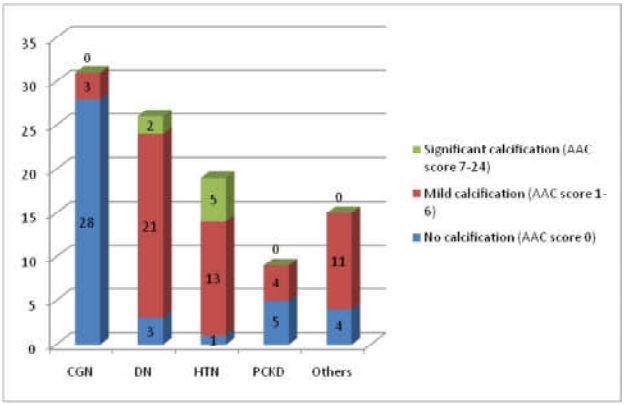

Fig. 4: *Vascular calcification status in various aetiological groups.*

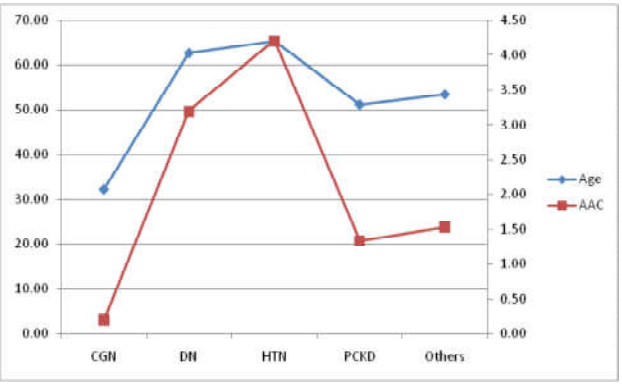

Fig. 5: *Showing co-variance of age and AAC score among different aetiological groups.*

Blood urea and serum creatinine levels correlated negatively with AAC score with correlation co-efficient of – 0.251 (p = 0.0118) and – 0.3081(p = 0.0018), respectively. CKD duration and serum cholesterol levels correlated positively with AAC score with p value of 0.0476 and 0.0287 respectively. However, in multiple regression test, all of these became non-significant, and only age remained as the single most important factor determining AAC.

Discussion

Secondary hyperparathyroidism is a well known complication of CKD. It imposes a significant burden on health and financial resources. Epidemiological studies have revealed a new trend towards the increasing prevalence of relative hypoparathyroidism in ESRD. This hypoparathyroid state is usually associated with adynamic bone disease (ABD), which is associated with increased cardiovascular mortality. Dialysis outcomes and practice patterns study (DOPPS), collecting data of dialysis patients in 11 countries, has shown the high prevalence of hypoparathyroidism in Asian countries like Japan, while more of hyperparathyroidism in European countries[4]. No data is available regarding status of predialysis patients of CKD stage 4 and 5. In this study, 34% of patients were found to be hypoparathyroid while 38% were hyperparathyroid. Group A had a higher mean serum iPTH levels than group B, which was statistically non-significant. However, subgroup analysis by chi-square test showed a significant trend towards hyperparathyroidism in conservatively managed patients, and hypoparathyroidism in dialysis group.

Apart from treatment strategy, age and aetiology of CKD were other significant risk factors found to be associated with PTH status. Our hypoparathyroid patients were elder than euparathyroid and hyperparathyroid patients and the difference was statistically significant. Similar findings were observed by Mehrotra *et al* in their study of dialysis patients who found a significant, inverse relationship between the age of the patients and serum iPTH levels[6]. Researchers suggest that this age-related decline is secondary to the lower serum phosphorus levels seen in elderly[7]. However, in our study we could not find any significant difference in serum phosphate levels in these groups. Another hypothesis is that plasma levels of pentosidine, an advanced glycosylation end product, progressively increase with advancing age. Panuccio *et al* showed an inverse relationship between serum pentosidine levels and serum iPTH[8]. This could probably be the reason for low serum iPTH levels in our elderly patients.

Two-thirds of our hypoparathyroid patients were diabetic. Diabetic patients usually have hypomagnesaemia a factor known to interfere with PTH synthesis. Also, studies with bovine parathyroid cell cultures have shown PTH inhibition with excess of glucose or deficit of insulin[9]. Adynamic bone disease in diabetic CKD patients has been explained by osteoblast apoptosis due to accumulation of advanced glycosylation end products[10].

The study showed a significant difference in corrected serum calcium levels among the 3 sub groups. Hypoparathyroid patients had a higher mean serum calcium level as compared to euparathyroid and hyperparathyroid patients. An inverse association between serum PTH levels and ionized calcium levels in haemodialysis patients has been reported earlier[11]. Hutchison *et al* described higher ionized calcium levels in ABD patients than in other types of renal osteodystrophy[12]. Epidemiological studies have pointed out chronic intake of calcium binders as well as

peritoneal dialysis with its higher calcium mass transfer, as risk factors for ABD.

The present study showed high prevalence of vascular calcification in CKD patients depicted by abdominal aortic calcification (AAC) score. The study revealed age, PTH status and aetiology of CKD to be significant factors associated with vascular calcification. Although duration of CKD, blood urea, serum creatinine and serum cholesterol levels also showed significant positive (duration and cholesterol) or negative (urea and creatinine) correlation in univariate linear regression analysis, these factors did not show any significant correlation in multiple regression analysis and age came out as the single contributory variable, significantly affecting the AAC score.

Among the categorical variables, PTH status and aetiology of CKD seemed to affect the vascular calcification in a way that age remained a common confounding factor in both of these analyses. Although hypoparathyroid patients showed a higher mean AAC score (2.53 ± 2.03), most of them had only mild vascular calcification and this trend of higher calcification did not reflect in the proportion of patients with 'significant' vascular calcification (3%) which remained almost equal to euparathyroid (3.5%) and much less than hyperparathyroid patients (13%). This asynchrony between mild and significant calcification in the hypoparathyroid patients might probably be due to the fact that hypoparathyroid patients were older than other 2 groups and age could be a confounding factor. On the other hand hyperparathyroid group had a lower mean AAC score than hypoparathyroid group but the proportion of patients with significant vascular calcification was much higher in this group. Considering the lower mean age of hyperparathyroid group than hypoparathyroid group, this much high prevalence of significant vascular calcification is definitely a noteworthy finding and indicates a contribution of PTH in pathophysiology of vascular calcification in CKD patients.

The results are in sharp contrast with previous Indian study which showed significantly higher prevalence of AAC in hypoparathyroid, as compared to hyperparathyroid, patients. (87.17% vs 57.89%, $p = 0.01$)[13]. It could probably be due to higher mean age of hypoparathyroid patients in that study which acted as a confounding factor and was later confirmed on multivariate analyses, when no association could be determined between parathyroid status and calcification.

Studies done in western and Japanese population have not found any association between vascular calcification and PTH status. Chertow *et al*[14] in their study of patients from USA and Europe, compared the progression of coronary artery calcification and abdominal aortic calcification between patients receiving calcium containing phosphate binders and patients receiving sevelamer, and did not find any significant differences in the progression of coronary artery calcification among calcium-treated subjects stratified by intact PTH but aortic calcification was more extensive in patients with above or below target values of iPTH than those within the target range. Our study has also shown significantly more extensive vascular calcification in diabetic nephropathy patients and hypertensive nephropathy patients than chronic glomerulonephritis and other groups of CKD. However, the PTH status also showed similar trend in diabetic patients with two-thirds patients of diabetic nephropathy hypoparathyroid, as compared to 23% in non-diabetic patients.

Conclusion

This study shows high prevalence of relative hypoparathyroidism and vascular calcification in CKD patients. This is the first Indian study giving a comparative assessment of parathyroid status between patients on haemodialysis and on conservative treatment. But, there were a few limitations. We looked at one time parathyroid hormone levels which, in fact, is a constantly changing variable and studies have found the time dependent PTH levels as predictors of mortality, which obviously could not be depicted in our study. However, the findings suggest that the current practice of over suppression of PTH needs to be revisited with regular monitoring of serum iPTH levels so as to detect the individual patient risk for developing adynamic bone disease and how that relates to bone loss and cardiovascular disease.

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"Saraswati is primarily a goddess of poetic inspiration and learning. She gets associated with the creator Brahma, as either his daughter or wife. In this role she is creative sound, which lends to reality a peculiar and distinctive human dimension – best described as coherent intelligibility."

– David Kinsley.

ANNOUNCEMENT

Invitation for Papers (Platform/Poster) for IACMCON-2017, Kolkata, West Bengal

Scientific papers are invited for Platform Presentation and Poster Presentation during IACMCON-2017 being held from 13th – 15th October, 2017

at ITC Sonar, Kolkata, West Bengal

The Poster Size should be 3 feet x 4 feet (approx.)

Prizes will be given for Best Platform Presentation and Best Poster Presentation.

The abstract of the paper should be mailed to:

raju_ys1197@yahoo.co.in

Mobile: 09440066482

The hard copy of the Abstract should be sent to:

Dr. Y. S. N. Raju

Chairman, Scientific Committee, IACMCON-2017

103 Ashoka Lake View Apts, Kundanbagh Begumpet, Hyderabad - 500 010

Last date for receiving the Abstracts is 31st August, 2017.

ORIGINAL ARTICLE

JIACM 2017; 18(2): 91-94

Effects of Glycaemic Status, HbA1c and Body Mass Index on Nerve Conduction Study in Pre-diabetics and Asymptomatic Diabetics

SH Talib, SR Bhattu**, Gaurav Punde***, Rohan Hegde***, Kulin Sheth***, Preetam Ahire****

Abstract

Background: The neuropathy associated with prediabetes is clinically similar to early diabetic neuropathy, with preferential injury of small nerve fibers resulting in pain and autonomic dysfunction. The neuropathic involvement per se is more relevant than diabetic glycaemic status. The observation signifies importance of knowing neuropathy, as endothelial dysfunction also could have taken place elsewhere which may be responsible for IHD and strokes.

Aim: To know the relationship of variables such as body mass index, fasting and post-meal blood sugar level, and HbA1c with nerve conduction parameters.

Methods: 60 age and gender matched cases of pre-diabetes, asymptomatic diabetes and healthy individuals were taken in the study. The nerve conduction in the tibial motor nerve, and sural sensory nerve were measured and electrophysiological changes were expressed in terms of changes in latencies, amplitude and velocity.

Results: The findings revealed that in pre-diabetic and asymptomatic diabetic groups BMI, fasting and post-proudial suger level and HbA1c were higher; sensory and motor nerve amplitudes were also found decreased. The result was statistically significant when compared to healthy group. The correlation with distal latency, and nerve conduction velocity was insignificant.

Conclusion: Hyperglycaemia, high BMI and elevated HbA1c are the important risk factors of onset of neuropathy alarming early consideration for undertaking lifestyle modifications for reversing/decreasing electrophysiological changes of neuropathy.

Keywords: Asymptomatic diabetes, BMI, HbA1c, pre-diabetes, peripheral neuropathy.

Introduction

The global prevalence of pre-diabetes has been increasing progressively in the past few decades. As per IDF Diabetes Atlas, the number of cases of IGT (2010) worldwide is estimated to be approximately 340 million. By 2030, the global prevalence of IGT is estimated to reach 8.4%, which will be approximately 462 million people[1,2]. It has been established that pre-diabetic status is a strong risk factor for overt diabetes and cardiovascular disease. It is generally agreed that all forms of diabetes pass through this pre-diabetic state before escalating into full-blown diabetes[3]. The commonly observed neuropathy in diabetics is distal symmetrical polyneuropathy (DPN) and has a prevalence of about 50%[4]. The presence of neuropathy in diabetics and/or pre-diabetics is associated with considerable morbidity, mortality and diminished quality of life. The neuropathy progresses from functional to structural changes in due course of time. So, timely identification and prompt management at pre-diabetic or early stages of diabetes before development of symptoms prevents further complications. A full understanding of risk factors predicting neuropathy is essential to better understand disease pathogenesis and develop effective prevention or treatment strategies. There are many risk factors responsible for pre-diabetes. These are associated with insulin resistance and are risk factors for the development of type 2 diabetes mellitus[5]. Higher prevalence of peripheral neuropathy, and predominantly small sensory fibre neuropathy, has been reported in subjects with metabolic syndrome, a condition that often includes pre-diabetes and obesity, and IGT in several other studies[6-9]. Nerve conduction studies are the most objective, accurate electro- diagnostic tests used to evaluate the electrical conduction of the motor and sensory nerves, and are reliable for detecting DPN. Diabetic peripheral neuropathy is associated with changes in nerve conduction velocity, amplitude and distal latency[10]. In the present study, the correlation between Body mass index (BMI), glycosylated haemoglobin (HbA1c), fasting (FSL) and post-meal (PSL) sugar levels with nerve conduction study (NCS) parameters (DL, Amp, NCV) were observed to be statistically significant.

Material and methods

Study design – cross-sectional study.

Study duration – 24 months. Study was conducted at MGM hospital, Aurangabad.

Sample size and inclusion criteria – total 180 cases, divided

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into three groups.

Group A: Healthy participants between age 20 - 70 years of both sexes who on clinical evaluation were not suffering from diabetes (n = 60).

Group B: Men and women aged 20 - 70 years having established diagnosis of pre-diabetes with or without signs of peripheral neuropathy (n = 60).

Group C: Men and women aged 20 - 70 years with asymptomatic diabetes (type-2) with or without clinical evidence of neuropathy (n = 60).

All the subjects were enrolled and categorised based on ADA 2014[11] criteria.

Diagnosis	Fasting plasma glucose	2-hour OGTT	HbA1C
Normal	< 100 mg/dl (5.6 mmol/l)	< 140 mg/dl (7.8 mmol/l)	< 5.7%
Pre-diabetes	100 - 125 mg/dl (5.6 - 6.9 mmol/l)	140 - 199 mg/dl (7.8 - 11.0 mmol/l)	5.7 - 6.4%
Diabetes	≥ 126 mg/dl (7.0 mmol/l)	≥ 200 mg/dl (11.1 mmol/l)	≥ 6.5%

Exclusion criteria

- Patients who denied consent to be a part of the study.
- Previous diagnosis of any systemic/infective/toxic/genetic/metabolic/inflammatory disease related to polyneuropathy.
- Patients consuming medications (phenytoin, antiretroviral, antitubercular) including diuretics and vitamins.
- Alcoholic patients.
- Patients of chronic kidney disease.
- Hyperthyroid or hypothyroid patients.
- Patients of macrocytic hypochromic anaemia.
- Skin lesions or swellings that would interfere with NCS.
- Patients who were critically ill.
- Patients having malignancy.
- Trauma to lower limbs of any kind.

Statistical analysis: Statistical analysis was done by using SPSS version 20th. All parameters are expressed in mean ± SD. For comparison of Quantitative data of three groups, ANOVA was applied. Tukey Post-Hoc test was also used for comparison of two groups. For comparison of healthy, pre-diabetic and diabetic subjects, unpaired t-test was applied. Chi-square test was also used to check significance of association between different groups and outcome of different variables. P-value was checked at 5% level of significance.

Results

In the present study, we compared the variables in different groups for evidence of peripheral neuropathy deduced on nerve conduction parameters, viz., distal latency, amplitude, velocity on tibial (motor) and sural (sensory) nerves.

Group A – Healthy, Group B – pre-diabetic, Group C – asymptomatic diabetic.

When we did a comparison of variables among pre-diabetics and asymptomatic diabetics, the mean values were seen increasing from healthy to pre-diabetics to asymptomatic diabetics in a graded manner. The values were statistically significant (p <0.0001) Table I.

Table I: Comparison of variables in groups A, B and C.

Variables	Group A (n = 60)	Group B (n = 60)	Group C (n = 60)	P value		
				Group A vs B	Group A vs C	Group B vs C
BMI (Kg/m^2)	21.74 ± 1.55	23.99 ± 2.47	26.69 ± 1.13	P < 0.0001 S	P < 0.0001 S	P <0.0001 S
HbA1c (%)	5.19 ± 0.21	6.10 ± 0.25	8.81 ± 1.78	P < 0.0001 S	P < 0.0001 S	P <0.0001 S
Fasting plasma glucose (mg/dl)	89.63 ± 6.48	113.80 ± 7.71	163.18 ± 36.40	P < 0.0001 S	P < 0.0001 S	P <0.0001 S
Post-prandial glucose level (mg/dl)	125.31 ± 8.77	173.85 ± 19.09	254.88 ± 54.49	P < 0.0001 S	P < 0.0001 S	P <0.0001 S

BMI – Body mass Index; S – significant.

In Table II, it can be seen that the amplitude of sensory and motor nerves is a more sensitive parameter for BMI, as compared to distal latency and nerve conduction velocity. The observation signifies that with increasing BMI, the amplitude of Sural SNAP and Tibial CMAP decreases bilaterally, and no correlation of BMI is observed with distal latency and NCV of sensory and motor nerves of either side.

Table II: Correlation of BMI with distal latency, amplitude and nerve conduction velocity.

NCS parameters	Nerve	BMI r-value	P-value
Distal latency	Sensory sural right	0.016	P = 0.830 NS
	Sensory sural left	0.025	P = 0.743 NS
	Motor tibial right	0.063	P = 0.397 NS
	Motor tibial left	0.038	P = 0.610 NS
Amplitude	Sensory sural right	- 0.165	P = 0.027 S
	Sensory sural left	- 0.309	P <0.0001 S
	Motor tibial right	- 0.342	P <0.0001 S
	Motor tibial left	- 0.425	P <0.0001 S
Nerve conduction velocity	Sensory sural right	- 0.001	P = 0.990 NS
	Sensory sural left	- 0.041	P = 0.583 NS
	Motor tibial right	- 0.193	P = 0.040 S
	Motor tibial left	- 0.076	P = 0.312 NS

However, in this study, the BMI and nerve conduction velocity of right motor Tibial nerve, were found to be correlated (p value = 0.040), as compared to other nerves. It is to be noted that the weak correlation (p value = 0.040) observed was because of wide variation in values of nerve conduction velocity in positive cases in the asymptomatic diabetic group noted in right motor Tibial nerve (4/60 patients having NCV < 40 m/s), as compared to the left side (1/60 patient having NCV < 40 m/s).

also for small fibre neuropathy. It is accepted that development of distal peripheral neuropathy in diabetes is dependent on multiple factors such as advanced glycation end products, oxidative stress, nitric oxide reactivity to blood vessels, polyol pathway, etc. Diabetes control and complications trial (DCCT) has supported the fact that in the peripheral neuropathies associated DM, hyperglycaemia is a common aetiologic mechanism. Pre-diabetes is linked with increased risk of vascular disease. There is an excess prevalence of coronary disease in those with fasting or post-load hyperglycaemia below the diabetic level[12,13]. Pathogenesis of pre-diabetics is linked to related insulin deficiency and tissue insulin resistance. Similarly obesity is an independent risk factor for cardiovascular diseases and diabetes mellitus due to release of pro-inflammatory cytokines from adipose tissue. Obesity causes insulin resistance and further neuropathy. In our study, the correlation between BMI, HbA1c, fasting and post-meal sugar levels with NCS parameters (DL, Amp, NCV); was depictive of inverse correlation, i.e., higher the values of variables; the amplitude of sensory, motor nerve decreased with normal distal latency on either side. The amplitude of sensory and motor nerves were found to be more sensitive parameters than velocity (Table II and III). The lesson we learn is that early lifestyle modifications may reverse the pattern of abnormal glycaemic status of asymptomatic diabetic patients back to pre-diabetic

Table III: Correlation between fasting sugar level, post-meal sugar level and HbA1c with distal latency, amplitude and nerve conduction velocity.

NCS parameter	Nerve	Fasting sugar level		Post-meal sugar level		HbA1c	
		r-value	P-value	r-value	P-value	r-value	P-value
Distal latency	Sensory sural right	0.104	P = 0.164 NS	0.108	P = 0.148 NS	0.008	P = 0.914 NS
	Sensory sural left	0.060	P = 0.423 NS	0.034	P = 0.653 NS	- 0.079	P = 0.292 NS
	Motor tibial right	0.060	P = 0.420 NS	0.062	P = 0.409 NS	0.044	P = 0.555 NS
	Motor tibial left	0.034	P = 0.655 NS	0.066	P = 0.381 NS	- 0.038	P = 0.613 NS
Amplitude	Sensory sural right	- 0.242	P = 0.001 S	- 0.282	P < 0.0001 S	- 0.193	P = 0.009 S
	Sensory sural left	- 0.280	P < 0.0001 S	- 0.294	P < 0.0001 S	- 0.223	P = 0.003 S
	Motor tibial right	- 0.434	P < 0.0001 S	- 0.393	P < 0.0001 S	- 0.369	P < 0.0001 S
	Motor tibial left	- 0.362	P < 0.0001 S	- 0.321	P < 0.0001 S	- 0.352	P < 0.0001 S
Nerve conduction velocity	Sensory sural right	- 0.006	P = 0.932 NS	- 0.030	P = 0.686 NS	- 0.045	P = 0.548 NS
	Sensory sural left	- 0.058	P = 0.440 NS	- 0.005	P = 0.944 NS	- 0.063	P = 0.401 NS
	Motor tibial right	- 0.083	P = 0.266 NS	- 0.073	P = 0.330 NS	- 0.034	P = 0.647 NS
	Motor tibial left	- 0.102	P = 0.175 NS	- 0.005	P = 0.943 NS	- 0.003	P = 0.966 NS

In the study, (Table III), the amplitude of sensory sural nerve, and motor Tibial nerve on either side shows positive correlation with FSL, PPSL, and HbA1c (p value = < 0.05 significant in all categories), and these are also inversely proportional to each other. However, distal latency, and nerve conduction velocity show no correlation with FSL, PPSL, and HbA1c) (p value = > 0.05 in all categories).

Discussion

Insulin resistance with prediabetes and diabetes is a part of the metabolic syndrome, which also consists of hypertension, hyperlipidaemia, and obesity. The individual components of the metabolic syndrome have been implicated as risk factors not only for cardiovascular and cerebrovascular disease but

status and normal.The results of our study were comparable with various authors who had reported hyperglycaemia and obesity as risk factors for neuropathy in early diabetics.

A study by Sumner CJ *et al*[6] has shown the deleterious effect of hyperglycaemia as confirmed by the occurrence of neuropathy associated with impaired glucose tolerance. They found neuropathy associated with pre-diabetes is milder than new onset diabetes, and small-nerve-fiber involvement is the earliest detectable sign of the neuropathy.The findings are in accordance with our study.

In a study by Munisekhar K *et al*[14] twenty diabetic patients and twenty health individuals, selected by random sampling technique, the authors estimated relationship between BMI, FSL, PPSL and HBA1c for all subjects and nerve conduction studies. They found that in the experimental group with rise in BMI, FBS, PPBS, HbA1c, sensory nerve conduction was decreased significantly when compared with control group. The observations correlate with our study.

In a study by Buschbacher RM[15] the effect of body mass index on nerve conduction study measurements of 253 subjects showed correlation between increased BMI and lower sensory/mixed nerve amplitudes, which again correlates with our study.

In a study by Chadhavineeta, Shivalkar Surendra S *et al*[16] on 90 subjects, the authors observed correlation between BMI and nerve conduction parameters and found that sensory nerve conduction amplitude decreases significantly with increase in BMI, whereas the effect on other parameters is non-significant. The observation on BMI parameter is in consistence with our findings.

In a study by Callaghan Brian C, Xia Rong *et al*[17] it was found that the prevalence of polyneuropathy was high in obese individuals, even among those with normoglycaemia. Diabetes, pre-diabetes, and obesity (BMI > 25 kg/m2) are the likely metabolic drivers of this neuropathy.The finding of this study correlates with the present study.

Conclusion

Body Mass Index, HbA1c, fasting and post-meal sugar levels were significantly raised in pre-diabetics and asymptomatic diabetics, when compared with healthy subjects.This study shows that sensory and motor nerve conduction amplitude decreases significantly with increase in BMI, HbA1c, fasting and post-meal sugar level, whereas the effect on other NCS parameters is non-significant.The sensory component appears early in pre-diabetics while motor nerve amplitude abnormality is observed late in course of disease, i.e., in asymptomatic diabetics.Thus, hyperglycaemia and obesity (BMI > 25 kg/m2) are strong risk factors in pre-diabetic and asymptomatic diabetic individuals causing sensory/motor neuropathy. Based on the results of the present study, it might be predicted that with better glycaemic and weight control, changes in peripheral neuropathy can be prevented in these subjects which ultimately has an impact on their cardiovascular morbidity and mortality.

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ORIGINAL ARTICLE

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Clinical and Biochemical Profile of Diabetic Ketoacidosis: An Observation of 120 Patients

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Abstract

Diabetic ketoacidosis (DKA) is the most common acute complication of diabetes mellitus. To evaluate the clinical spectrum of patients with DKA, we performed a study in the post-graduate department of Medicine of Sarojini Naidu Medical College, Agra. The study population comprised 120 patients of DKA. Out of 120 patients, 80 were of T1DM and 40 were of T2DM. The mean age of patients was 37 ± 7.3 years. The most common precipitating factor was discontinuation of insulin in T1DM and pulmonary tuberculosis in T2DM. Most common clinical manifestation was nausea and vomiting (50%), followed by dehydration (48.33%), abdominal pain (37.5%). Patients were investigated and managed accordingly. Overall mortality was 6.67%.

Keywords: Diabetic ketoacidosis (DKA), diabetcs mellitus (DM).

Introduction

Diabetic ketoacidosis (DKA) is the commonest acute complication of diabetes. DKA typically complicates T1DM, but can sometimes affect patients with T2DM[1].

Most patients with T1DM with DKA have either an absolute or near absolute deficiency of insulin[1,2]. However, most patients with T2DM who develop DKA due to stress or intercurrent illness have measurable, even increased, though relatively deficient, insulin level[1,3].

The most common precipitating factors are infections, and discontinuation of insulin therapy[4,5]. Other less common precipitating factors include stroke, myocardial infarction, trauma, pancreatitis, alcohol and drug abuse[5]. Pathophysiology of DKA involves decreased level of insulin and increased concentration of counter regulatory hormones (catecholamines, cortisol, glucagon, growth hormone). This imbalance leads to hyperglycaemia[5]. The purpose of this study was to know the clinical profile and precipitating factors of DKA patients.

Material and methods

This study was undertaken in the post-graduate department of Medicine, SN Medical College, Agra. 120 patients of T1DM and T2DM who were in DKA, admitted from OPD and emergency.

Patients were classified into T1DM or T2DM, on the basis of their clinical profile and medical records. patients underwent thorough history and clinical examination and accordingly investigated. Diaganosis of DKA was made with random blood sugar level > 250 mg/dl, an arterial pH of less than 7.35, serum bicarbonate value < 15 mEq/l with a moderate degree of ketonemia and /or ketonuria[6].

Result

In our studty, a total of 120 patients were included, out of which 80 patients were of type 1 DM and 40 were of type 2 DM . Among 120 patients of DKA, 65 were male and 55 were female, male to female ratio was 1.18 : 1.00 .

Table I: Sex distribution of patients of DKA.

Gender	Distribution of cases	Percentage
Male	65	54.17
Female	55	45.83

The age of patients ranged from 15 - 70 years with a mean age of 37 ± 7.3 years.

Table II: Age distribution of patients with DKA.

Age (years)	No. of patients	Percentage
15 - 30	27	22.5
31 - 40	34	28.3
41 - 50	24	20.0
51 - 60	22	18.3
> 60	13	10.9
Total	120	100

The most common precipitating factor was discontinuation of insulin in T1DM (37.5%), followed by UTI (22.5%), pneumonia (18.7%) and pulmonary tuberculosis (15.0%).

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Table III: Precipitating factors of DKA in T1DM.

Precipitating factor	No. of patients	Percentage
Discontinuation of insulin	30	37.5
UTI	18	22.5
Pneumonia	15	18.7
Pulmonary tuberculosis	12	15.0
Others	5	6.3

In T2DM the most common precipitating factor was pulmonary tuberculosis (40.0%), followed by discontinuation of oral hypoglycaemic agents (OHA) and insulin (25%) and pneumonia (17.5%).

Table IV: Precipitating factors of DKA in T2DM.

Precipitating factor	No. of patients	Percentage
Pulmonary tuberculosis	16	40.0
Discontinuation of OHA and insulin	10	25.0
Pneumonia	7	17.5
UTI	3	7.5
Others	4	10.0

Clinical manifestations were analysed and it was seen that nausea and vomiting was seen in 60 (50.0%) patients, dehydration was seen in 58 (48.33%), 45 (37.5%) patients presented with abdominal pain and 40 (33.33%) patients presented with polyuria/polydipsia.

Table V: Clinical manifestations of patients with DKA.

Clinical manifestation	No. of patients	Percentage
Nausea/vomiting	60	50.0
Dehydration	58	48.33
Abdominal pain	45	37.50
Polyuria/polydipsia	40	33.33
Kussmaul breathing	38	31.66
Hypotension	30	25.0
Altered sensorium	6	5.0
Others	20	16.66

Investigations in T1DM showed mean blood glucose was 410 ± 62 mg/dl. Serum Na^+ was 129 ± 6 mmol/l, serum K^+ 3.8 ± 1.1 mmol/l, blood urea 48 ± 10 mg/dl, serum creatinine 1.6 ± 0.6 mg/dl, arterial pH 7.14 ± 0.10.

Investigations in T2DM patients showed mean blood glucose 515 ± 46 mg/dl, serum Na+ 130 ± 5.0 mmol/l, serum k^+ 4.1 ± 0.6 mmol/l, blood urea 53 ± 8 mg/dl, serum creatinine 1.7 ± 0.5 mg/dl, arterial pH 7.3 ± 0.06.

Table VI: Investigation profile in T1DM and T2DM.

Investigations	Values in T1DM	Values in T2DM
Blood glucose (mg/dl)	410 ± 62	515 ± 46
Serum Na^+ (mmol/l)	129 ± 6	130 ± 5.0
Serum K^+ (mmol/l)	3.8 ± 1.1	4.1 ± 0.6
Blood urea	48 ± 10	53 ± 8
Creatinine	1.6 ± 0.6	1.7 ± 0.5
Arterial pH	7.14 ± 0.10	7.3 ± 0.06

Discussion

In our study, out of a total of 120 patients 80 (66.67%) were of T1DM and 40 (33.33%) were ofT2DM. A study at a large academic centre observed that 21.7% patients had T2DM[7]. In a study conducted by Seth *et al*[8], 80% patients of DKA were of T2DM. S Mishra has reviewed the pathogenesis of ketosis prone T2DM and showed that DKA is not exclusively seen in T1DM but can also be seen in T2DM[9].

Nausea and vomiting were the most common manifestations (50%) of DKA patients in our study followed by dehydration (48.33%). 37.5% of patients were complaining of polyuria and polydipsia. 33.33% patients were having abdominal pain. Only 31.66% patients were having kussmaul breathing Similar symptomatology was also seen in previous studies by Munro *et al*, Umpierrez *et al* and Adhikhari *et al*[10,11,12].

In this study the commonest precipitating factor in T1DM was discontinuation of insulin (37.5%), followed by UTI (22.5%). Pneumonia was responsible for precipitating DKA in 18.7% and pulmonary tuberculosis was involved in 15% cases. The most common precipitating factor in T2DM was pulmonary tuberculosis (40%), followed by pneumonia (25%), UTI (17.5%) and discontinuation of anti-diabetic drugs (7.5%).

Previous studies have also shown that infection at any site is an important precipitating factor in DKA[13-16]. Adhikari *et al*, showed diabetic foot as the precipitating factor for DKA in 30.23% of patients[10].

The overall mortality in the present study was 6.67%, which is similar to the other studies. Westphal found mortality of 5.1%[15]. Beigelman and Faich *et al* found mortality of 9%[17,18]. Adhikari *et al* found mortality rate 16.3% and Matoo *et al*, found 23.7% of mortality[10,14].

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ORIGINAL ARTICLE

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Retrospective Appraisal of Endoscopic Data and Association of *H. Pylori*

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Introduction

H. pylori, a spiral gram-negative bacterium has a global prevalence. In spite of a long association with humans it is not a commensal[1]. There are a number of modes of transmission, the most common being the faecal-oral route. Crowded habitations, poor hygiene and sanitation promote *H. pylori* transmission. Its prevalence in India is very high; >= 80% in rural setting[1]. Effective eradication regimens are readily available. However, increasing drug resistance and ease of reinfection make it vital to check for recurrences.

Many patients undergoing upper gastro intestinal (UGI) Endoscopy (UGIE) present with dyspeptic symptoms. A majority of Indian patients solicit specialist care, usually when symptoms persist despite use of over-the-counter (OTC) symptomatic therapy.

Aims and objectives

Through an audit of UGIE records at a busy clinic in a metropolitan city, we have tried to highlight issues that if addressed, could probably help improve data collection and aid current research in *H. pylori* prevalence, and its treatment, with possible implications on patient care.

Material and methods

This retrospective observational study, conducted at the endoscopy unit of Remedy Clinic, Kolkata involves collation of UGIE data, from patients scoped for dyspeptic symptoms, gathered over the previous 3 years. Patients found urease positive (by Helicochek® on two antral biopsy specimens) had a follow-up (FU) UGIE after a ten day course of *H. pylori* eradication therapy with Proton Pump Inhibitor (PPI), clarithromycin and amoxicillin.

Among the patients assessed, exclusion from the study was deemed fit if: (i) the patient was on PPI for a non-GI cause that could not be withdrawn, (ii) the patient was on a PPI for a GI cause, but was non compliant to advice to withhold the same for a period of at least 2 weeks, (iii) the patient did not return for FU at or shortly after the prescribed duration, (iv) the patient could not complete therapy, (v) the patient had to be prescribed an alternative regimen.

Observations

We audited UGIE data of 467 patients. 213 (46%), found positive on Rapid Urease Test (RUT), were started on therapy and advised FU at 4 weeks. Of these 213 patients, 19 (8.9%) presented either within the next 7 - 10 days or more than 8 weeks after procedure and were excluded from the study. 91 (42.7%) presented at 4 weeks (+/- 3 days), while 12 (5.6%) presented between 5 - 8 weeks. These 103 patients (48.3% of 213, 22% of 467) were included in the study. On occasions, FU at the prescribed time was missed due to operator unavailability.

Of the patients attending the clinic with dyspeptic symptoms (580), 467 were endoscoped. Of these, all had previously, in the recent past been on some or the other form of acid suppressive therapy (AST), predominantly taken OTC, but occasionally also on medical advice. 224 patients were not on any form of AST at presentation. Of the 356 that were, 92 (25.8%) were receiving AST for non-GI problems, most of them prescribed. They were excluded from the study. 264 (74.15%) were on AST for GI complaints, and a significant proportion was taking the drugs OTC. This group was advised to withhold the drugs and 177 (49.7%) of them complied with the advice. The remaining 87 (24.4%) that did not, were excluded from the study. Even among those included, long-term PPI use largely had the effect of confounding endoscopic findings. Collection of subject contact details was routinely practised. Compliance monitoring, by encouraging calendar marking, reproduced at follow-up was not practised. The same data entry personnel had assisted in gathering data, and UGIE was performed by a single person. Hence operator variability was negated.

There were no changes to the data collection format used during the said period.

The success rate of the eradication protocol returned satisfactory results. However, multiple FU visits would probably help in assessing relapse/recrudescence patterns. Suggestions for, whether in subsequent follow-up visits, invasive assessment could be warranted, remain out of bounds of this study.

This study does not include those symptomatic patients who had been started on therapy empirically, those who

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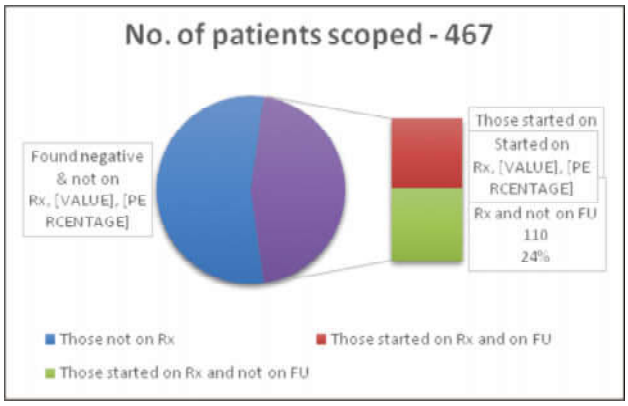
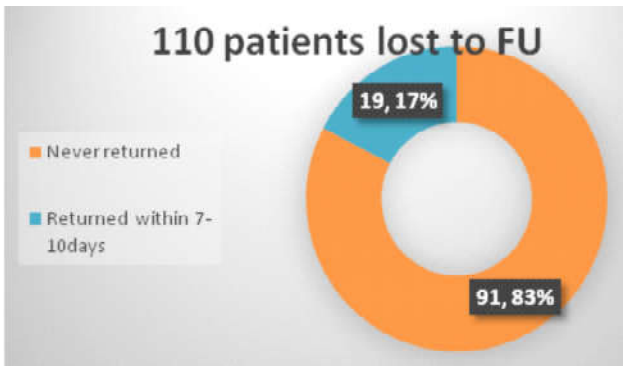
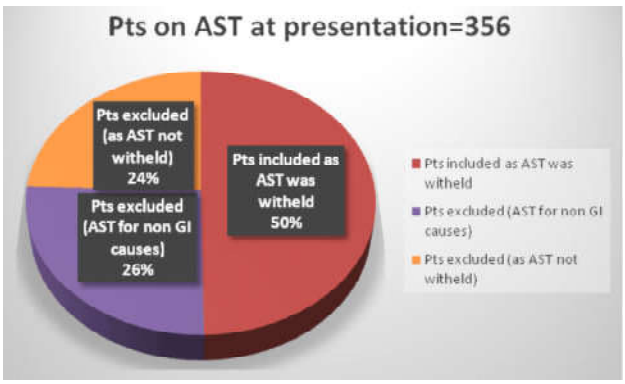
refused UGIE, or those urease negative patients who had merely been given acid suppression.







Review of literature

Most experts are of the opinion that the moment an infection is detected, attempts must be made to eradicate it. This however, might be easier said than done, especially in developing countries[1].

In view of the widespread prevalence of *H. pylori*, and a range of possible clinical effects, guidelines have been established to determine that population of patients who must receive treatment, segregating them from those that might possibly benefit from therapy. The American College of Gastroenterology guidelines of 2007[2], the Asia Pacific Consensus of 2009 and the Maastricht-Florence Consensus conference of 2012 make several such recommendations. While they are unanimous in their recommendation to treat patients who have Peptic Ulcer Disease or Gastric Mucosa Associated Lymphomas, and post "endoscopic resection of early gastric cancer", there are discrepancies in other suggestions[3].

"Uninvestigated dyspepsia" has been defined as endoscopy naïve dyspeptic symptoms, as seen in primary care, and is one of the areas of discord between the various recommendations. Other grey zones include, but are not limited to, 'Functional dyspepsia'[3].

An Indian study[4] from the late 1990s presents interesting revelations. The author reports confounding endoscopic findings associated with unchecked, over-the-counter use of H2 Receptor Blockers (H2RBs) and Proton Pump Inhibitors (PPIs). Also, empirical use of *H. pylori* eradication "kits" were occasionally found to alter the real colonisation status of patients presenting with dyspeptic symptoms. However, interestingly, a substantial number of patients in that study returned urease positive in spite of having been on H2RBs/PPIs/eradication "kits" and despite having largely unremarkable endoscopic findings. The relevance of this "old" study appears heightened in the present day as we continue to face rampant use of H2RBs/PPIs globally. The significance is stark in India, where the disease is endemic and drug resistance more prevalent.

Clarithromycin is one of the component drugs in the commonest 1st-line regimen. Hence, Clarithromycin resistance is an important factor that must be considered while planning treatment. If present, it is deemed to be absolute, with no benefit of a higher dose or longer duration of therapy. Prior exposure to macrolides appears to be an important determinant for possible clarithromycin resistance. However, the "sequential therapy" seems to offer better cure rates, despite containing clarithromycin, even in patients known to be carrying a resistant strain.

Barring the issue of compliance, Bismuth based (and frequently a second-line) regimen has been found effective in situations of resistance to both clarithromycin and metronidazole[5].

There is no established recommendation requiring all patients to be tested after attempted eradication. Neither has any established method of testing been unequivocally recommended ahead of the others[6]. Thirumurthi and Graham[1] have opined against routine endoscopic surveillance in order to minimise risks of iatrogenic reinfection.

Confirmation of eradication is mandatory for patients who

have received treatment for *H. pylori* associated peptic ulcer disease and Mucosa Associated Lymphoma[2,5] and post-endoscopic resection of early gastric cancer associated with *H. pylori* infection[2]. A section of experts recommend repeat testing even for persistent symptoms in patients treated with eradication therapy for dyspepsia[2,5]. It is agreed however, that persistence of symptoms does not necessarily indicate that a patient remains infected. They hence recommend confirmatory testing in case a repeat course of antibiotics is contemplated[5].

Serum *H. pylori* antibody detection is not a useful test for confirming eradication, as antibodies could persist long after the organism has been eradicated[2,5,6].

Rapid urease test, as used in our center, is a highly specific test. However, as with any other modality of testing, it is affected by use of PPIs, antibiotics and should ideally be coupled with another test, in the post-treatment phase. PPIs should hence be withheld for 1 - 2 weeks before testing[2,5], in which situation it can even be used as the sole diagnostic investigation[2]. As such, a four week interim is recommended between therapy and repeat testing[2,5].

Discussion

Guidelines relating to treatment with a view to eradicate, in Peptic Ulcer Disease or Gastric Mucosal Lymphomas, are unambiguous.

However many Indian patients presenting with 'uninvestigated' or 'functional' dyspepsia are likely to carry the organism, often without an ulcer, the so called "Non Ulcer Dyspepsia". So, some physicians opt against offering treatment, considering ease of re infection. Hence in patients treated solely for symptomatic dyspepsia, FU UGIE for persistent symptoms should probably be situation specific.

The RUT is fairly reliable. Yet, in view of international recommendations, it could be coupled with a second test when FU testing is required, albeit with a documented informed consent. Financial constraints are a major barrier to this. A 4 week interval to FU, and a minimum 2 week gap in PPI use prior to diagnostic testing should be stressed on. This is difficult as AST is freely available.

If possible, patients failing a scheduled FU, should be contacted.

Data collection is to be more stringent. A history of prior macrolide exposure should be sought and documented. In endemic regions (including travel to an endemic zone), it is difficult to rule-out repeat infections and recrudescence, the latter implying drug resistance. Also, differentiating between the two continues to remain a grey area.

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"You should forget the mistakes of the past,
just drop it and move ahead.
You are not the same person you were in the past
when you committed those mistakes,
you have changed."

– Sri Sri Ravi Shankar.

ORIGINAL ARTICLE

JIACM 2017; 18(2): 101-04

Comparative Analysis of Ultrasound Guided Percutaneous Needle Aspiration and Percutaneous Continuous Catheter Drainage as Part of Management of Uncomplicated Amoebic Liver Abscess at a Tertiary Centre in Northern India

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Abstract

Introduction: Amoebic liver abscess can be treated with either percutaneous needle Aspiration (PNA) or continuous catheter drainage (CCD) and both methods have advantages and disadvantages. Various studies have shown discrete results regarding preference for one over the other. We evaluated both methods to determine the better modality of treatment.

Aims and objectives: To compare PNA and CCD as part of management of uncomplicated amoebic liver abscess. The end points studied were: (1) Success rate, (2) Time needed for clinical improvement, (3) Time needed for 50% reduction of abscess, (4) Time needed for total reduction of abscess (size < 3 cm), and (5) Duration of hospital stay.

Methodology: The study was done at SN Medical College, and patients were confirmed radiologically and serologically by IgM Elisa method. Patients who had uncomplicated abscess(es) [no features of rupture, impending rupture (liver tissue rim > 1 cm), no compression effect and abscess size > 3 cms diameter] were included and randomised to two groups of 20 patients, each who were subjected to PNA and CCD and results were analysed on the basis of study criteria.

Results: It was found that, in CCD group, success rate was higher, time needed for clinical improvement, time needed for 50% reduction, total reduction and hospital stay was lesser than in PNA group.

Conclusion: It can be concluded that continuous catheter drainage, using pigtail catheter, leads to rapid clinical improvement and resolution of abscess and appears to be the better option for treating uncomplicated amoebic liver abscess.

Keywords: Liver abscess, aspiration, pus.

Introduction

In developing countries like India, water borne diseases and protozoal diseases are common. Amoebic infections are common, especially in the Doab region of northern India. Amoebic liver abscess is the most frequent extra-intestinal manifestation of *Entamoeba histolytica* infection. Various treatment modalities for treatment of amoebic liver abscess include medical therapy (amoebicidal drugs) alone or combined with ultrasound (USG) guided needle aspiration/ percutaneous catheter drainage/open drainage. Instead of open drainage, USG guided intermittent percutaneous needle aspiration (PNA) and continuous catheter drainage (CCD) in combination with amoebicidal drugs are now widely accepted and, considered safe and effective methods for management of uncomplicated liver abscesses. Both PNA and CCD have their pros and cons and yet there is no guideline for nonsurgical management of amoebic liver abscess.

Aims and objectives

The study was a comparative analysis of USG guided PNA and CCD as part of management of uncomplicated amoebic liver abscess in a tertiary centre in Northern India. The end-points studied were: (1) Success rate, (2) Time needed for clinical improvement, (3) Time needed for 50% reduction of abscess, (4) Time needed for total reduction of abscess (size < 3 cms), and (5) Duration of hospital stay.

Material and methods

The present study was done at SN Medical College, Agra, from January, 2013 to November, 2014 and patients diagnosed with amoebic liver abscess radiologically and serologically (by IgM Elisa method) were included in the study. Patients who had uncomplicated abscesses with no features of rupture, impending rupture (liver tissue rim > 1 cm), no compression effect and abscess size > 3 cms

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diameter were included in the study. Those having multiple abscesses, ruptured/impending rupture, symptoms and signs of peritonitis or size of abscess less than 3 cms in maximum diameter were excluded from the study.

Methodology

A total of 40 patients were recruited and randomly allocated into two groups. Group A patients were aspirated under continuous real time sonographic guidance using standard protocols (PAN group) and, in group B, a pigtail catheter of appropriate size was introduced in the abscess cavity using Seldinger technique (CCD group). The catheter was removed when output dropped to < 10 ml/24 hrs for 2 consecutive days.

Patients in PNA group who did not improve clinically after first aspiration, or showed refilling of the abscess cavity on follow-up sonography, were subjected to a second aspiration on 4th day. Failure of patients to improve after a second aspiration was considered as failure of aspiration therapy at the 3rd USG done on 7th day, and these patients were subjected to catheter drainage (however, these patients were not included in the catheter drainage group).

The patients were examined weekly for one month, monthly for the next three months and two-monthly thereafter, until complete resolution of the abscess was achieved.

Treatment was considered successful when patient improved clinically (i.e., subsidence of fever and local signs and symptoms), and follow-up imaging showed resolution of the abscess (total resolution or reduction in size to < 3 cms diameter).

Observations

Among 40 patients, 20 patients randomised to group A were treated with percutaneous needle aspiration (PNA) and 20 patients randomised in group B were treated with continuous catheter drainage (CCD).

In PNA group, two patients developed signs of rupture. They were managed surgically (open drainage) and excluded from the study. Rest of the patients were subjected to repeat USG on 4th day. In these 18 patients, 10 patients showed reduction of cavity size with clinical improvement; rest 8 patients were re-aspirated on 4th day.

When USG was done on 8th day on these of 8 patients, 3 improved but 5 patients were found to have increase in size of abscess cavity. They were then subjected to catheter drainage.

13 of 20 patients in the PNA group were treated successfully by PNA alone. Total reduction in size of abscess cavity was achieved in 6 - 26 weeks.

USG guided CCD was done in group B (n = 20). On the first day, CCD was done along with metronidazole therapy. All patients subjected to this therapy improved with a success rate of 100%. Total clinical improvement was seen in 3 - 8 days. In all patients, regular monitoring of patients with serial USG was done on 4th and 7th day. 50% reduction in cavity size was seen in 4 - 12 (mean 6.94 ± 2.79) days. Total duration of hospital stay of the patients was 5 - 22 (mean 9.94 ± 4.45) days.

Table I: Success rate in different groups.

Parameter	Treatment groups				P value
	Needle aspiration (n = 20)		Catheter drainage (n = 20)		(by chi-square test)
	No. of patients	Value	No. of patients	Value	
Success rate	13	65%	20	100%	0.0008

Table II: Time needed for clinical improvement in both groups.

Parameter	Group A	Group B	P value (by chi-square test)
No. of days (mean ± SD)	5.60 ± 1.35	4.63 ± 1.63	0.004

Table III: Time needed for 50% reduction in cavity size.

Parameter	Group A	Group B	P value (by chi-square test)
No.of days (mean ± SD)	9.4 ± 5.67	6.94 ± 2.79	0.002

Table IV: Time needed for total reduction in cavity size.

Parameter	Group A	Group B	P value (by chi-square test)
No. of weeks (mean ± SD)	10.5 ± 3.66	9.88 ± 5.5	0.03

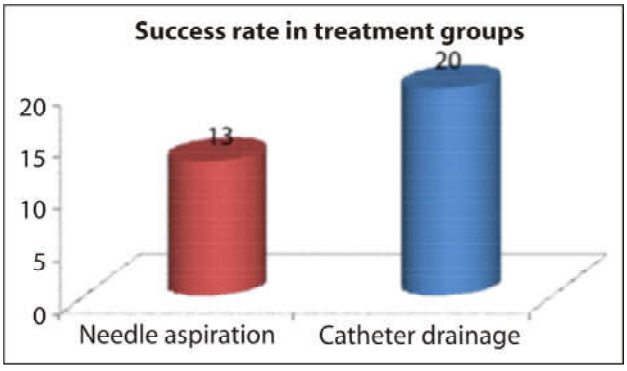

Fig. 1: *Success rate in treatment groups.*

Fig. 2: *Time needed for clinical improvement.*

Table V: Duration of hospital stay in both groups.

Parameter	Group A	Group B	P value (by chi-square test)
No. of days (mean ± SD)	12.3 ± 4.57	9.94 ± 4.45	0.03

Discussion

Our study was aimed at comparing the clinical outcome of two widely used methods of pus drainage for amoebic liver abscess; i.e., PNA versus CCD, both in combination with metronidazole.

In patients who had undergone PNA, the overall success rate was 65%. In first aspiration, it was 50% which increased to 65% in second aspiration.The success rate in other studies varied from 79 to 100%[1-4].

In a study conducted by Rajak *et al* (1998)[5], the success rate was 60%. They concluded that the higher response rate achieved in previous studies was due to repeated aspiration, even 3 - 4 times, in few cases. But in their study a repeat aspiration was done only in case of no response to the first aspiration. However, subjecting the patients to multiple needle aspirations over a short period, as done in above studies, is traumatic and unpleasant for the patient and may not be acceptable. Moreover, multiple attempts at aspiration do not guarantee a 100% cure rate.

Zerem *et al* (2007)[6] considered a third attempt of PNA as failure of treatment after two aspirations. Only one of the 11 aspirations was successful on the third attempt which confirmed that further needle aspiration is rarely successful in case of no response to first aspiration.

For these reasons we opted to subject the patient to CCD after failure of second aspiration. In our study, CCD had a success rate of 100%. Clinical improvement was measured by number of days from the day of admission.

One important reason for failure of needle aspiration was

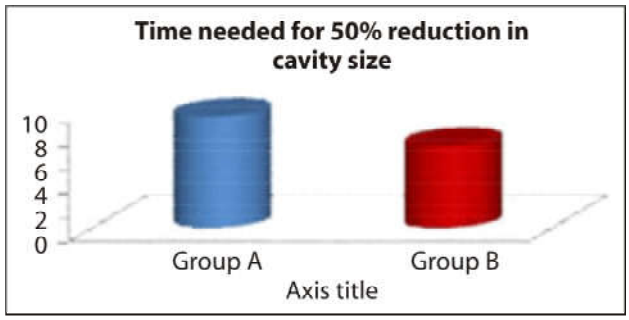

Fig. 3: *Time needed for 50% reduction in cavity size.*

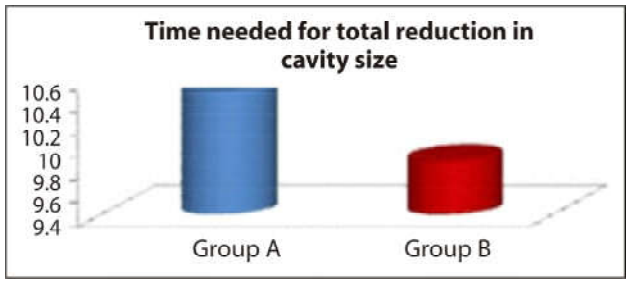

Fig. 4: *Time needed for total reduction in cavity size.*

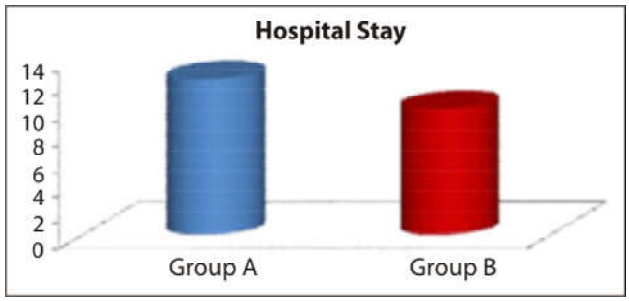

Fig. 5: *Duration of hospital stay.*

inability to completely evacuate the thick viscous pus that may be present in some of the abscesses[2-7]. Rapid re-accumulation of abscess after needle aspiration is another problem[4].

In contrast to PNA, placement of an indwelling catheter provides a continuous drainage. Hence, incomplete evacuation and re-accumulation are not associated with catheter drainage[5,7,8,9].

In comparing interventional studies, both percutaneous needle aspiration and catheter drainage are safe for non-surgical treatment of liver abscess. But catheter drainage is more effective than needle aspiration. CCD appears to be better in terms of duration to achieve relief, duration of medical therapy and complete resolution of cavity.

Conclusion

Patients subjected to percutaneous needle aspiration had

a lower success rate than those who were drained using a Pigtail catheter. Complications such as re-accumulation and increase in cavity size were seen in percutaneous needle aspiration group. In needle aspiration group, time needed for 50% reduction and time needed for total reduction of abscess size, both, were greater than for those abscesses drained using pigtail catheter. Moreover, repeated aspirations were required in some cases in needle aspiration group. It can be concluded that drainage using pigtail catheter leads to rapid clinical improvement, rapid resolution of abscess, and appears to be the better option for treating uncomplicated amoebic liver abscesses.

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"Live in harmony and concord.
Be organised and cooperative.
Speak with one voice and
make your resolutions with one mind.
...you will not falter to execute your duties."

– RIG VEDA.

REVIEW ARTICLE

JIACM 2017; 18(2): 105-9

Scrub Typhus During Dengue Outbreak in Delhi: A Case Series and Review of Literature

Prabhat Kumar, Riyaz Charaniya**, Anindya Ghosh**, Ratnakar Sahoo***, Srinivasa Murthy****, Sakshi Mittal**

Abstract

The year 2015 witnessed yet another outbreak of Dengue in Delhi. Maximum number of cases were recorded between the months of September and November. Acute febrile illness with thrombocytopenia is the most common presentation of Dengue fever. However, there are several other causes of fever with thrombocytopenia and Scrub Typhus is one of them. We diagnosed 6 cases of Scrub Typhus in our medical unit during this dengue season. We present these cases alongwith a review of literature on Scrub Typhus.

Keyword: Eschar, thrombocytopenia, ARDS, MODS.

Introduction

Scrub Typhus (ST) is a mite-borne febrile illness and was believed to be a rural disease. But in the last decade, it has been reported from various parts of the country, including Delhi. The clinical manifestations can range from an acute febrile illness to PUO, with multiorgan involvement. ST is a close differential diagnosis of Dengue fever and is, commonly, missed. The purpose of this article is to make readers aware about this disease entity, as early diagnosis and treatment can decrease morbidity, and mortality significantly.

Case reports

Case 1

A 20-year-old girl, pursuing B. com in Delhi native of Uttarakhand, presented with chief complaints of fever for 10 days and breathlessness for 8 days. Fever was intermittent, moderate grade, associated with chills but no rigors. Breathlessness was insidious in onset and gradually progressive and was associated with dry cough. She had visited her native place two weeks prior to onset of symptoms. She was given oral antibiotics by a local doctor, but her symptoms did not abate. On physical examination: Pulse rate - 110/min, BP - 80/50 mmHg, respiratory rate (RR) - 24/min and temperature was 101° F. An eschar was noted on right side of the neck (Fig. 1). Fine crepitations were heard over right axillary and mammary region.

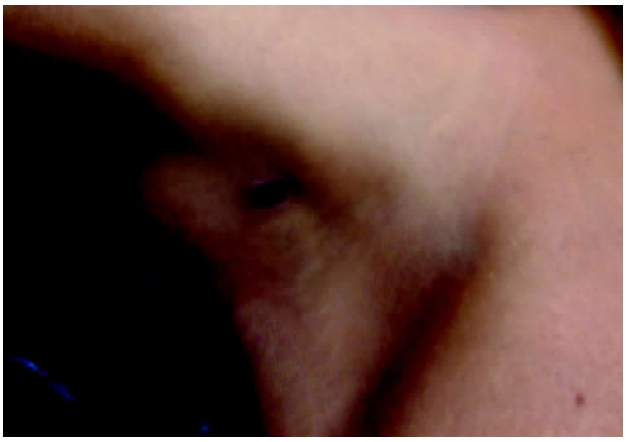

Fig. 1: *An eschar over the neck.*

ABG analysis was suggestive of type 1 respiratory failure, pH - 7.35, PaO_2 - 50 mmHg, Spo2 of 76%, $PaCO_2$ -38 mmHg and HCO3 - 18.6 mmol/l. Haemogram showed; ESR - 62 mm/hr, Hb - 7.8g/dl, TLC - 13,400/cumm (N84, L16) and platelet count - 80,000/cumm. Renal and liver function tests were mildly deranged; urea - 60 mg/dl, creatinine - 1.3 mg/dl, bilirubin - 4.1 mg/dl, SGOT - 98 IU/L, SGPT - 125 IU/L. Chest X-ray showed patchy reticular opacities in right lower

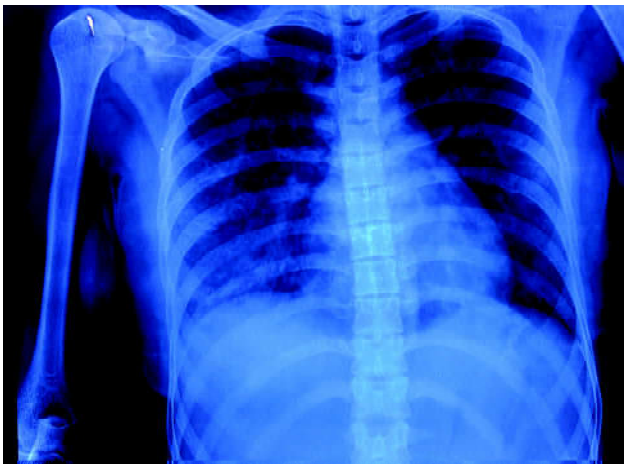

Fig. 2: *Patchy reticular opacities in the right lower zone, suggestive of atypical pneumonia.*

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zone (Fig. 2). Tests for malaria, dengue and leptospirosis were negative. IgM ELISA for Scrub Typhus was positive. She was empirically started on broad spectrum antibiotics and doxycycline, alongwith inotropic support. However, she had to be intubated and put on mechanical ventilation on first day of admission itself due to persistent hypoxaemia. She later developed ARDS, refractory shock with MODS and succumbed to her illness on the third day of admission. Here, a delay in diagnosis lead to ARDS and mortality.

Case 2

A 60-year-old lady, resident of Uttarakhand, presented with chief complaints of fever for one month which was intermittent, mild to moderate grade, associated with chills and used to subside after taking antipyretics. On physical examination: Pulse rate - 130/min, BP (systolic) - 70 mmHg, RR - 20/min and temperature - 100.8° F. There were multiple enlarged lymph nodes in right cervical and axillary region. An eschar was noted over right arm (Fig. 3). She had mild pitting pedal oedema and, on auscultation, air entry was reduced in left infrascapular region.

Blood investigations showed: Hb -10 gm/dl, TLC - 3,000/cumm and platelet count - 60,000/cumm. Renal function tests, serum electrolytes and urine microscopy were normal but liver function tests (LFT) were mildly deranged (Bil - 0.5 mg/dl, SGOT - 151 IU/L, SGPT - 118 IU/L, albumin - 1.8 gm/dl). ECG showed RBBB pattern and chest X-ray revealed cardiomegaly with mild pleural effusion on left side. She was started on inotropes for low blood pressure and broad spectrum antibiotics, alongwith Doxycycline, were started from day 1 of admission. Serological tests for dengue, malaria and leptospirosis were negative but IgM ELISA for Scrub Typhus came positive. Pleural fluid examination showed a transudative picture. A 2D Echocardiography was done which showed hypokinesia of anterior and anterolateral wall with an ejection fraction of 30%. She showed considerable improvement and ionotropes were discontinued on fifth day of admission and was discharged on tenth day. Platelet count on the day of discharge was 1.5 lac/cumm and all other biochemical parameters were normal. Here, ST presented as prolonged pyrexia and should be suspected in patients of PUO with thrombocytopenia.

Case 3

A 65-year-old gentleman, resident of Delhi, shopkeeper by occupation with no recent travel history, came to our emergency with chief complaints of fever and burning micturition for 1 week. Fever was intermittent, low grade and without any chills or rigors. He also had 2 - 3 episodes of vomiting in last 2 days. He was admitted in a private hospital before coming to our hospital where he received intravenous broad spectrum antibiotics but his symptoms persisted. On physical examination: pulse rate - 100/min, BP - 100/60 mmHg, RR - 16/min and temperature - 99° F. Rest of the systemic examination was essentially normal. A provisional diagnosis of UTI (urinary tract infection) was made and relevant investigations were sent.

Haemogram showed: Hb - 10.7 gm/dl, TLC - 8,000/cumm and platelet count - 60,000/cumm. Renal function tests were grossly deranged (urea - 117 mg/dl, creatinine - 2.2 mg/dl). LFT were also deranged; bilirubin - 0.9 mg/dl, SGOT - 131 IU/L, SGPT - 36 IU/L and serum albumin - 2 gm/dl. Urine microscopy showed 4 - 6 pus cells and culture grew *E. Coli* which was sensitive to Colistin. Chest X-ray and ECG were normal. He was given intravenous broad spectrum antibiotics as per culture sensitivity but his symptoms persisted. On the third day of admission, when he was undressing, an eschar was seen near left axillary region by one of the resident doctors (Fig. 4). Doxycycline was immediately added to his treatment regime and serology for Scrub Typhus was sent, which came positive. Serology for malaria, dengue and leptospirosis were negative. On fifth day of admission he went into shock and inotropes

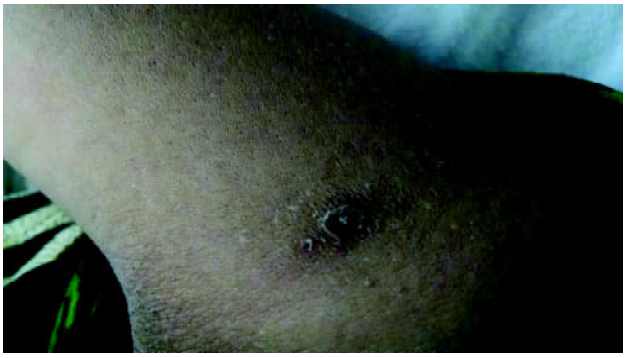

Fig. 3: *An eschar over the right arm.*

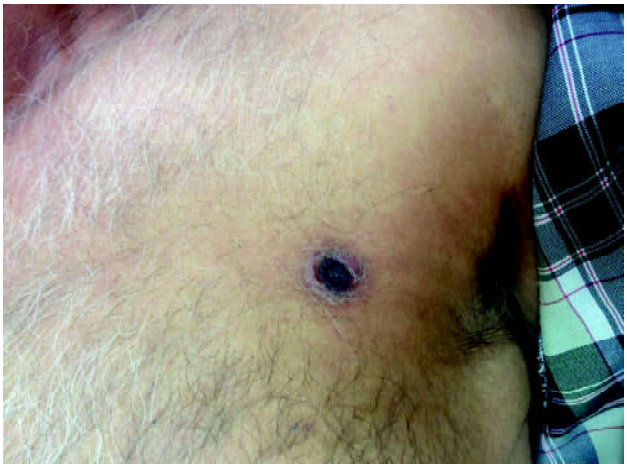

Fig. 4: *An eschar near the left axilla.*

were started. Next day morning, he suddenly developed spontaneous nasal bleeding; platelet count was done and found to be < 20,000/cumm. Multiple units of platelet concentrates were transfused but his bleeding persisted. He developed refractory shock with MODS and passed away on the eighth day of admission. Here, ST complicated UTI leading to catastrophic outcome.

Case 4

A 51-year-old lady, resident of Delhi, with no recent travel history, presented with chief complaints of fever for 1 week which was continuous, high grade and associated with vomiting. She was admitted in our hospital a month back for a week and a diagnosis of Dengue fever was made. According to her discharge slip, she had presented with complaints of fever for 4 days and had two episodes of hematemesis. Blood investigations, in her previous admission showed, platelet count of 20,000/cumm and Dengue serology IgM by ELISA was positive. She was transfused platelet concentrates in her earlier admission and was discharged on 4th day with a platelet count of 1 lac/cumm and in afebrile state. After 3 weeks of her discharge, she again developed fever and came to us. On examination: Pulse rate - 104/min, BP - 110/70 mmHg, RR - 16/min and temperature -104° F. Rest of the systemic examination was essentially normal and no eschar was seen. Haemogram showed: Hb - 10.3 gm/dl, TLC - 6,000/cumm and platelet count - 50,000/cumm. Renal and liver function tests were normal. Blood and urine culture were sterile. IgM for Dengue was again positive (it can remain positive for atleast 4 - 6 weeks) and tests for malaria and leptospirosis were negative. We thought of Scrub Typhus as we could not find a cause for this episode of fever and thrombocytopenia. Serology for scrub typhus was sent and doxycycline was started empirically. To our surprise, she became afebrile within 48 hours and her platelet count after 2 days was 1.2 lac/cumm. ST serology too came positive. Patient was discharged on day 5 and is doing well. This case shows how clinical response to doxycycline can be used to diagnose ST.

Case 5

A 40-year-old gentleman, resident of Delhi, tailor by occupation with no history of recent travel, presented with chief complaints of fever for 8 days which was high grade, intermittent and associated with chills but not rigors. His wife told us that she had noticed a black colored skin lesion over his back. On examination: Pulse rate - 110/min, BP - 120/80 mmHg, RR - 18/min and temperature - 102° F. A large eschar was seen over his back (Fig. 5). Rest of the systemic examination was essentially normal. Haemogram

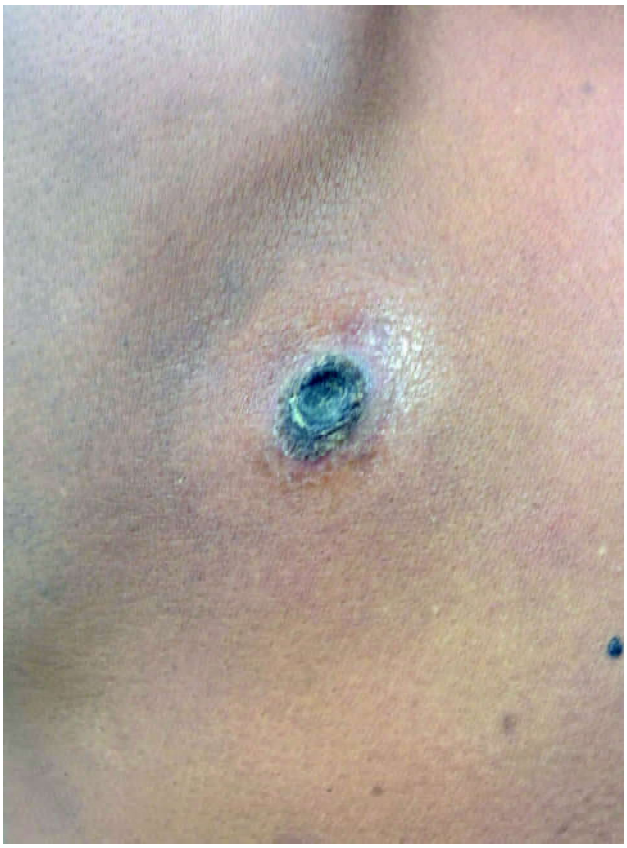

Fig. 5: *A big eschar over the back.*

showed: Hb - 11.2 gm/dl, TLC - 7,400/cumm and platelet count - 75,000/cumm. Renal and liver function tests were absolutely normal. Serology for malaria, dengue and leptospirosis were negative. IgM for ST was positive. He was treated with oral doxycycline and his fever subsided within 2 days and was discharged in stable condition.

Case 6

A 32-years-old male, native of Delhi, a shopkeeper by profession with no recent travel history presented to the medical emergency with complaints of high grade intermittent fever with headache and chills for 6 days. He also had breathlessness for 5 days which was initially exertional and rapidly progressed such that he was breathless even at rest. He was admitted in a private hospital on the 3rd day of his illness and was treated with empirical antibiotics for bilateral pneumonitis, but to no improvement. He was subsequently referred to our hospital as a suspected case of H1N1 influenza.

On examination, he was conscious and oriented. Pulse rate - 120/min, BP - 90/60 mmHg. RR - 36/min, SpO2 - 75% on room air and temperature of 102° F. Chest examination revealed bilateral infrascapular fine end-inspiratory crackles

with no other significant finding on systemic examination. Blood investigations showed: ESR - 6 mm 1st hour, Hb -10.2 gm/dl, TLC-4500/cu mm (N55 L50), platelet count- 1,00,000/cumm. LFT was deranged; bilirubin - 1.3 mg/dl, SGOT - 239 IU/L, SGPT - 149 IU/L, ALP - 412 IU/L. ABG was suggestive of ARDS; pH - 7.36, PaO_2 - 52 mmHg $PaCO_2$ - 38 mmHg and PaO2/FiO2 < 200. Chest X-ray showed evidence of B/L lower zone interstitial infiltrates corroborated on a CECT thorax done subsequently (Fig. 6). Dengue serology and throat swab for H1N1 were negative. However, his serum samples tested positive for IgM antibodies against scrub typhus, following which, antibiotic regime was changed and doxycycline was added. He was intubated and kept on mechanical ventilation for ARDS slowly weaned following improvement, and discharged on the 10th hospital day. Atypical pneumonia is common in ST and should be suspected if there is coexisting thrombocytopenia or transaminitis.

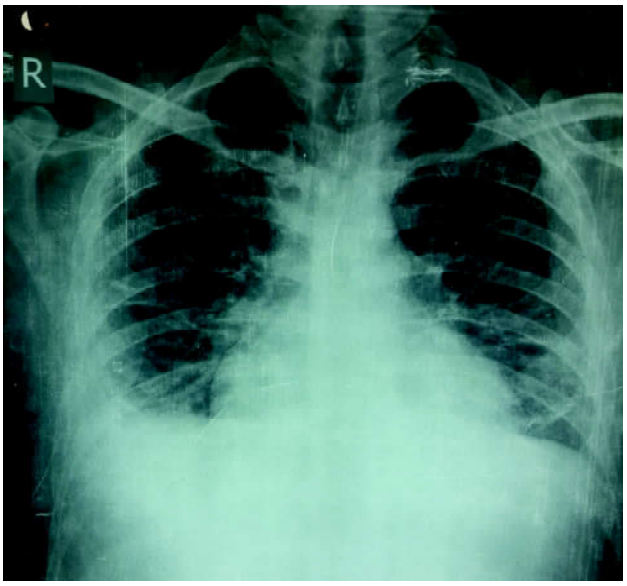

Fig. 6: *Bilateral lower zone interstitial infiltrates.*

Discussion

Scrub Typhus (ST) is a mite-borne acute febrile illness caused by *Orientia tsutsugamushi*. Scrub means vegetation and typhus means 'fever with stupor'. Term "mushi" means mite or insect and "tsutsugamushi" means small and dangerous. Scrub typhus is endemic in the "tsutsugamushi" triangle which includes India too[1]. In the last few years, there have been several outbreaks of ST in India. There are reports of ST from south, north, north-western and north-eastern part of the country[2-5]. *O.tsutsugamushi* is an obligate intracellular gram-negative coccobacillus which is transmitted to humans by the bite of larval mites (chiggers). Humans are accidental hosts and infection is maintained in larval mites by transovarian transmission. The symptoms generally occur 7 - 10 days after the bite of an infected chigger. The clinical manifestations can range from a simple undifferentiated fever to severe life-threatening disease[6].

The most common clinical manifestation is fever, headache and myalgia. Almost half the patients have a non-pruritic macular or maculopapular rash. Eschar is a necrotic skin lesion at the site of infected chigger bite and is pathognomic of ST. Several studies in India have shown varying prevalence of eschar in their series. 13% patients had an eschar in a case series from south India, whereas, no eschar was found in a case series from north western India[7-8]. In our series, 4 patients had eschar. Generalised tender lymphadenopathy with hepatosplenomegaly can be present in ST. Only one patient in our series had lymphadenoapathy and hepatosplenomegaly was not seen in any patient. Thrombocytopenia is common in severe illness and all 6 patients in this series had moderate-to-severe thrombocytopenia (Table I). Other febrile illnesses associated with thrombocytopenia are malaria, dengue and leptospirosis. Leukopenia or leukocytosis can occur. In our series one patient had leukocytosis, one had leukopenia and remaining 4 had normal leukocyte count. Acute kidney injury (AKI) and elevated liver enzymes are commonly seen. Here, 2 patients had AKI and 4 had deranged liver function tests.

Severe ST is commonly complicated by refractory shock, heart failure, interstitial pneumonitis with ARDS and meningoencephalitis. Multiple organ dysfunction (MODS) is another common complication of ST and causes significant mortality when associated with meningoencephalitis or ARDS. 2 patients in our series had ARDS, one patient expired and one recovered. 2 patients developed MODS due to ST. The mortality rate of ST ranges from 0 - 30% in untreated patients, depending on strain virulence and patient condition[9]. ARDS is a serious complication, and has a high mortality rate.

Diagnosis of ST is often delayed due to lack of awareness and unavailability of diagnostic tests. Early diagnosis and treatment significantly decreases morbidity and mortality[6]. Weil-Felix test is most commonly performed in India but it has low sensitivity and specificity. Weil-Felix test shows false negative results in first week of illness and is positive in second week. IgM ELISA is easy to perform and has good sensitivity and specificity.

Doxycycline 100 mg twice daily for 7 - 15 days is the recommended therapy. Patients of ST become afebrile within 48 hours of starting therapy and this response can be used to diagnose ST cases. Alternatively azithromycin 500 mg for 3 days can be used, especially in pregnant

Table I: Clinical Profile of scrub typhus patients.

Clinical profile	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Native place	Uttarakhand	Uttarakhand	Delhi	Delhi	Delhi	Delhi
Fever duration	10 days	30 days	7 days	7 days	8 days	6 days
Associated symptoms	Breathlessness	Nil	Dysuria/vomiting	Vomiting	Rash	Breathlessness
Eschar	Present	Present	Present	Absent	Present	Absent
Renal function	Deranged	Normal	Deranged	Normal	Normal	Normal
LFT (Bil/SGOT/PT)	4.1/98/125	0.5/151/118	0.9/131/36	Normal	Normal	1.3/239/149
Platelet count (cumm)	80,000	60,000	60,000	50,000	75,000	1,00,000
TLC (cumm)	13,400	3,000	8,000	6,000	7,400	4,500
Dengue serology	Negative	Negative	Negative	Positive	Negative	Negative
Scrub Typhus serology	Positive	Positive	Positive	Positive	Positive	Positive
Treatment	Doxycycline	Doxycycline	Doxycycline	Doxycycline	Doxycycline	Doxycycline
Complication	ARDS/MODS	Shock	Shock/MODS	Nil	Nil	ARDS
Outcome	Death	Recovered	Death	Recovered	Recovered	Recovered

women[10]. Chloramphenicol is another option but is less commonly used due to serious adverse effects.

Conclusion

All internists should be aware of this disease entity, which closely mimics dengue and malaria. There are certain points which can help in diagnosing ST easily. An eschar is the hallmark of ST and all clinicians should look for it, especially in the hidden areas of the body. In complicated malaria there is anemia, leucopenia and thrombocytopenia. Dengue fever has leucopenia, hemoconcentration and thrombocytopenia with serositis. Thrombocytopenia is frequent in ST and is commonly associated with leukocytosis. The positive predictive value for diagnosis of ST is 80% when thrombocytopenia, leukocytosis and elevated hepatic enzymes are combined[11]. Doxycycline is widely available and should be empirically started whenever there is suspicion of ST.

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UPDATE ARTICLE

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A Comparison of Aerosol Delivery Devices

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Introduction

An aerosol is defined as liquid or solid particles suspended in a carrier gas. Delivering drugs directly to the lungs reduces systemic adverse effects and results in a higher drug concentration in the target airways. While the principles of inhalational therapy were elucidated only in the previous century, the use of drugs for respiratory diseases via inhalation has a history of at least 4,000 years.

Traditional Ayurvedic medicine dating back to 2000 BC includes Datura preparations, containing alkaloids with bronchodilator properties, which were made into pastes that could be dried and smoked through a pipe. Most other ancient native cultures also describe remedies for asthma that were inhaled and include plants with anticholinergic properties like datura, henbane and belladonna. The 19th and 20th centuries resulted in the appearance of various devices for the delivery of inhaled compounds to the lungs including ceramic inhalers, nebulisers, asthma cigarettes and powders, hand-bulb nebulisers and compressor nebulisers – some of which were of doubtful efficacy and utilised compounds of questionable safety.

Aerosolised drugs are now an important part of treatment of patients with asthma. Inhaled bronchodilators and corticosteroids are used as primary therapy in the treatment of both asthma and chronic obstructive pulmonary disease and are administered by devices that include nebulisers, metered-dose inhalers and dry powder inhalers. The number of devices now available are many and may be confusing to both patients and clinicians. Each of these devices has specific advantages and disadvantages, though all of them have been shown to be effective in most situations. Inhaled drugs are available in multiple inhaler systems. This paper discusses the features of various aerosol devices available and the principal involved in their selection and use[6].

Asthma and COPD guidelines recommend individualising inhaled therapy for each patient, taking into consideration patient preference. However given the confussing array of available devices it becomes important that health care providers and patients have a basic knowledge of working of various devices[7],[8].

Advantages of aerosol therapy[9]

Inhaled aerosol medications for the treatment of pulmonary diseases have several advantages:

a. Compared to oral or parentral route, very little doses required.

b. High concentration in lungs achieved, despite very low dose, so efficacy is greater.

c. Reduced systemic side-effects due to very low dose.

d. More rapid onset of action.

e. Some drugs are only active with aerosol delivery, e.g., cromolyn, ciclesonide for asthma and dornase alpha for cystic fibrosis.

f. Painless and convenient.

Principle of inhalation therapy[10]

Drug delivery into the respiratory system takes place by three main methods – gravitational sedimentation, inertial impaction, and diffusion. Large particles are deposited by the first two mechanisms in the airway, while the smaller particles make their way into the peripheral regions of the lung (alveoli and terminal bronchioles) by diffusion.

Factors which directly influence the aerosol deposition by above three mechanisms, are aerodynamic size distribution of the aerosol particles, and density of the aerosol particles. Apart from these factors, other determinants are nature of the propellant, device being used, technique of device use pharyngeal and lower airway anatomy, severity of obstruction, hygroscopic properties of aerosol, and speed of inhalation.

Where does an inhaled aerosol drug go?[11-14]

Lung deposition is 10 to 20 per cent for most aerosol systems. For example, of two hundred micrograms of albuterol in two actuations or puffs from an MDI, only about twenty to forty micro-grams reach the lungs even with correct technique. The remaining drug is lost in the oropharynx, the device, the exhaled breath, and the environment.

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Determinants of aerosol characteristics[15]

a) Inhaler device
b) Technique of use
c) Airway disease severity
d) Drug particle size
e) Propellant
f) Density of aerosol particle
g) Formulation lipophilicity and hygroscopicity
h) Plume speed and duration
i) Inspiratory flow inhaled and volume breath hold
j) Device acceptance and adherence
k) Extremes of age

Inhaler device[16-18]

Review of RCTs comparing inhaler devices report no difference in efficacy between devices.

Technique of use[19]

It is true that patients use their inhaler incorrectly. Efficient inhalation technique was demonstrated by only 46 - 59 per cent of patient in studies reviewed by Cochrane. The mean percentage of people who used their devices correctly found to be 63 per cent for MDIs, 75 per cent for breath actuated MDIs and 65 per cent for DPIs. Poor technique can be associated with a marked (up to 50 per cent) decrease in the amount of drug deposited in the lung. A slow and deep inhalation with co-ordination is a good technique for MDIs whereas a rapid and forcible inhalation is needed for DPIs. A faster inhalation with MDIs leads to oropharyngeal deposition, especially of larger particles.

Airway disease severity

Severe disease disallows the use of DPIs as sufficient inspiratory flow is not possible.

Particle size[20,21]

Smaller particles (less than 1 micron) are distributed throughout the lung, reach distal airways and are responsible for high pulmonary deposition of around 60 per cent. 10 per cent get exhaled and 30 per cent are deposited in the oropharynx. Particles of size 1 - 5 micron are deposited in large and conductive airways. Particles more than 5 micron tend to settle in the mouth and oropharynx.

Propellant

HFA propellant is better than CFC as it overcomes many issues associated with CFC MDIs including priming, temperature effects, tail off and plume geometry.

Speed of inhalation[22-24]

A faster inhalation rate increases the likelihood of oropharyngeal deposition with an MDI. Large particles tend to settle in the oropharyngeal region with fast inhalation whereas smaller particles show little difference in lung and oropharyngeal deposition, whether inhalation is fast or slow.

Hygroscopicity

DPIs, particularly, are sensitive to moisture and their storage in a dry place is very important, otherwise its efficacy goes down considerably.

Extremes of age

Children less than 5-year-old and some elderly patients should not be prescribed DPIs because they can not generate sufficient Inspiratory effort.

Aerosol devices

Aerosol devices are divided into:

Metered-dose inhalers

a. With spacer
b. Without spacer
c. Soft mist inhaler
d. Breath actuated MDI

Dry powder inhalers

a. Diskhaler
b. Turbuhaler
c. Aeroliser
d. Handihaler

Nebulisers

a. Ultrasonic
b. Jet
c. Mesh

Any device could be used in any patient however there are some limitations for certain sets of people like DPIs cannot be used in children less than 5 years of age or in elderly patients with very low inspiratory flow. Similarly, MDIs and DPIs cannot be used in comatose and intubated patients. NAEEP guidelines recommend selection of aerosol devices according to age of the patient.

Age-based recommedations for use of aerosol delivery device types (NAEPP guidelines)[25].

Aerosol system	Age
Small volume nebuliser	≤ 2 years
Metered-dose inhaler	> 5 years
MDI with holding chamber/spacer	> 4 years
MDI with holding chamber/spacer and mask	≤ 4 years
Breath-actuated MDI, (e.g., Autohaler)	> 5 years
DPI	≤ 5 years

MDI (Metered dose inhaler)

It contains the drug mixed with a propellant, usually hydrofluroalkane (HFA), in a sealed cannister with a metering valve and stem into an actuated boot. After volatilasation of the propellant the final volume emitted from the MDIs is 15 - 20 μl/dose. The MDI can be actuated as frequently as every 15 seconds. The lung deposition ranges from 10 - 25% of the nominal dose in adults. MDIs no longer contain the ozone-depleting chlorofluorocarbon (CFC) propellants and are either HFA-solutions or HFA-suspension devices. HFA-solution MDI have a smaller drug particle size and achieve greater lung deposition than HFA-suspension MDI which have large particle sizes.

Spacer devices are an extension attachment to the MDI and simply provide a space and distance between the patient's mouth and inhaler device to slow down the high velocity of the emitted aerosol cloud. This leads to reduced throat deposition and allows time for greater evaporation of the propellant, leading to relatively smaller drug particles that have greater potential to deposit within the lung.

Soft mist inhalers have been developed that have a slow moving aerosol spray and smaller particle size. There is therefore less potential for local side-effects (example oral candidiasis from corticosteroids) and for systemic absorption by swallowing the dose.

Breath-actuated MDIs detect the beginning of the patient's inhalation and trigger the inhaler at that point to insure synchrony. As these devices require a mechanical trigger to actuate the device upon inspiration, a flow rate of approximately 30 l/min is necessary which may be a limitation with patient with severe airflow obstruction. These devices overcome some of the most common limitations of MDIs.

MDI inhalers require slow and deep inhalation as well as co-ordination. The most important aspect of inhalation techniques is a slow (less than 60 litre/minute and deep inhalation. This lasts for two seconds in children and 5 seconds in adults. Failure to use a slow and deep inhalation is the most common mistake made by patients using MDI and is more common than failure of co-ordination.

Differences in characteristics between CFC and HFA MDIs.

Physical component	CFC	HFA
Delivery of dose		
From a near-empty canister	Variable	Consistent
With variable ambient temperature	Variable	Consistent (to -20°)
Spray		
Force	Higher Impaction	Lower (3 times)
Temperature	Colder	Warmer (approx.30° C)
Volume	Higher	Lower
Taste	Different from HFA	Different from CFC
Breath-hold	Less important with CFC	More important with HFA
Priming	Important following short period of nonuse	Longer time of nonuse allowed without priming

Steps for correct use of metered-dose inhaler (MDI) and breath-actuated MDI (Autohaler).

MDI technique

1. Hold the MDI to warm it to body temperature.
2. Remove the mouthpiece cover.
3. Inspect the mouthpiece for foreign objects.
4. Shake the MDI well (3 or 4 shakes).
5. If the MDI is new or has not been used recently, prime it by shaking and pressing the cannister to deliver a dose into the air. Repeat several times.
6. Breathe out normally, away from the MDI.
7. Open the mouth and keep the tongue from obstructing the mouthpiece.
8. Hold the MDI upright, with the mouthpiece aimed at the mouth.
9. Place the mouthpiece between the lips or 4 cms (2 fingers) in front of the widely opened mouth.
10. Breathe in slowly and press the MDI cannister down once at the beginning of inhalation.
11. Continue to inhale until the lungs are full.
12. Move the mouthpiece away from the mouth and hold breath for 5 to 10 seconds (or as long as comfortable).
13. Wait for at least 15 - 30 seconds between doses.
14. Repeat for the prescribed number of doses.

15. Recap the mouthpiece.
16. If using corticosteroid MDI, gargle and rinse the mouth with water or mouthwash after completing the dose.

Cleaning the MDI (once a week and as needed)

1. Look at the hole where the medicine sprays out from your inhaler. Clean the inhaler if you see powder in or around the hole.
2. Remove the metal cannister from the mouthpiece.
3. Set the cannister aside so it does not become wet.
4. Clean the plastic parts of the device using mild soap and water. (Never wash the metal cannister or put it in water).
5. Let the plastic parts dry in the air, (e.g., overnight).
6. Put the cannister back inside the mouthpiece and replace the cap.
7. Test the MDI by releasing a puff into the air.

Cleaning the Autohaler (once a week and as needed)

1. Remove the mouthpiece cover.
2. Turn the autohaler upside-down.
3. Wipe the mouthpiece with a clean dry cloth.
4. Gently tap the back of autohaler so the flap comes down and the spray hole can be seen.
5. Clean the surface of the flap with a dry cotton swab.
6. Recap the mouthpiece and make sure the lever is down.

Advantages and disadvantages of holding chambers or spacers ("add-on" devices) used in conjunction with metered-dose inhalers.

Advantages

1. Reduced oropharyngeal drug impaction and loss.
2. Simplifies co-ordination of MDI actuation and inhalation.
3. Allows use of MDI during acute airflow obstruction with dyspnoea.

Disadvantages

1. Large and cumbersome compared to the MDI alone.
2. Additional expense required.
3. Some assembly may be needed.
4. Patient errors include firing multiple puffs into chamber prior to inhaling, or delay between actuation and inhalation.
5. Possible contamination with inadequate cleaning.

Steps for correct use of MDI with a holding chamber/ spacer.

Spacer valve holding chamber technique

1. Hold the MDI to warm it.
2. Assemble the apparatus and check for foreign objects.
3. Take the cap off of the inhaler mouthpiece.
4. Attach the MDI to the holding chamber/spacer.
5. Shake the MDI (3 or 4 shakes).
6. Hold the cannister in a vertical position.
7. Breathe out normally.
8. Open the mouth and keep the tongue from obstructing the mouthpiece.
9. Place the mouthpiece into the mouth (or place the mask completely over the nose and mouth).
10. Press the MDI cannister once and simultaneously breathe in slowly through the mouth.
11. If the device produces a "whistle", inspiration is too rapid.
12. Allow 15 - 30 seconds between puffs.
13. Move the mouthpiece away from the mouth and hold breath for 10 seconds (or as long as comfortable).
14. The technique is slightly different for a device with a collapsible bag: Open the bag to its full size. Press the MDI cannister immediately before inhalation and inhale until the bag is completely collapsed (can breathe in and out of the bag several times to evacuate the medication).
15. The technique is slightly different if a mask is used with a child. Place the mask over the child's mouth and nose, making sure the mask fits snugly against the face, keeping the child's head level. Holding the mask in place, push down once on the top of the inhaler. Hold the mask in place while the child takes 6 normal breaths (inhales and exhales 6 times). Remove the mask from the child's face.
16. Repeat for the prescribed number of doses.
17. Rinse the mouth if using inhaled steroids.

Clean the Holding Chamber (every 2 weeks and as needed)

Chamber device:

1. Disassemble the device for cleaning.
2. Wash in clean warm soapy water; rinsing is optional.
3. Drip-dry over night.

4. Do not towel dry the spacer as this will reduce dose delivery because of static charge.
5. Reassemble the spacer after it is dry.

Dry powder inhalers[26,27]

DPIs are propellant free and usually contain powdered drug particles that are bound to a large carrier such as lactose. The efficacy of DPIs is highly dependent on patients' Inspiratory effort; high inhalation flows (sometimes as high as 60 liters per minute) are needed to de-aggregate drug from the lactose carrier molecule and achieve optimal drug delivery to the lung. This is why it is not good for children below five years of age, elderly and severe disease with poor inspiratory effort.

DPI requires rapid and forceful inhalation. Failure to use fast inhalation from the start through a DPI results in limitation of efficacy. They require sufficient inspiratory flow > 60l/min that cannot be achieved by children and patients with severe airflow obstruction. Humidity is also a concern as it causes powder clumping and reduced dispersal of the particle mass.

DPIs are breath actuated so they reduce the problem of coordinating inspiration. Patients are instructed to exhale outside the device to prevent blowing of the drug.

Steps for correct use of dry powder inhaler (DPI)

1. Twist and remove cap.
2. Hold inhaler upright (mouthpiece up).
3. Turn grip right, then left, until it clicks.
4. Breathe out normally; do not exhale into the device.
5. Place the mouthpiece into the mouth and close lips tightly around the mouthpiece.
6. Inhale dose with a rapid and steady flow; inhaler may be held upright or horizontal during inhalation.
7. Remove the mouthpiece from the mouth and hold breath for 10 seconds (or as long as comfortable).
8. Be sure not to exhale into the device.
9. Replace the cover and twist to close.
10. Store the device in a cool dry place.
11. When a red mark appears at the top of the dose indicator window, there are 20 doses remaining.
12. When the red mark reaches bottom of the window, the device is empty and must be replaced.

Nebuliser

Ultrasonic and jet nebulisers are commonly used in clinical practice. Ultrasonic nebulisers work by using high frequency vibration directed at the drug liquid in order to generate aerosol clouds for inhalation. Jet nebulisers use high velocity pressurised air directed through a narrow venturi opening over the surface of the drug liquid to produce aerosol for inhalation within the nebulising chambers.

A new significant innovation was made in the nebulisers market around 2005, with creation of the ultrasonic vibrating mesh technology (VMT). With this technology a mesh/membrane with 1,000 - 7,000 laser drilled holes vibrate at the top of the liquid reservoir, and thereby pressure out a mist of very fine droplets though the holes. This technology is more efficient than a having a vibrating piezoelectric element at the bottom of liquid reservoir.

Nebulisers require no special technique for use and tidal breathing is sufficient for administering the drug. They can be used at any age and in almost any situation regardless of the disease severity or acuity. It is also possible to mix several medications and deliver them simultaneously to the patient. Very high doses can also be given via nebulisers to the patient, an important advantage over other devices. Though unproven, nebulisers also promote confidence in the patient as it generates visible mist that reassures the patient. Another advantage of nebulisers is that they contain no propellants that can damage the atmosphere and require little nor no teaching.

The disadvantages include a lack of portability and lengthy treatment times and are therefore less favoured than MDIs and DPIs. They require properly fitting face masks, require periodic cleaning and contamination is possible. Some medications are unavailable in a preparation that can be nebulised and some preparations available in suspensions do not aerosolise well. There is also variability of performance efficiency among different nebulisers and the amount of drug available for lung deposition is not predictable, unless a particular drug in a particular formulation is studied with a device. As compared to other delivery devices, nebulisers are much less efficient and result in greater amount of drug wastage. Nebulisers are also more expensive than either MDIs and DPIs, especially ultrasonic nebulisers limiting their use as commonly prescribed therapies.

It is useful in the very young, very old, debilitated or distressed and intubated patients. An inspiratory pause is not required for efficacy and drug concentration can be modified.

A number of factors determine the efficiency of a nebuliser system including the respirable dose, nebulisation time, dead volume of the device and the gas used to drive the nebuliser.

Respirable dose: It is the most important characteristic of nebuliser performance and is dependent on the mass output of the nebuliser and the size of the particles produced. Droplet size should be 2 - 5 microns for airway deposition and 1 - 2 microns or smaller for parenchymal deposition.

Nebulisation time: Time required to deliver a dose of medication. In general, the greater the volume of drug to be delivered and the lower the flow rate of driving gas, longer the nebulisation time. Treatment is complete when the nebulisation begins sputtering.

Dead volume[28]: Volume of medication trapped inside the nebuliser, and therefore not available for inhalation. It is about 1 - 3 ml . Increasing the amount of the solution with in the nebuliser up to 4 - 6 ml reduces the proportion of drug lost as dead volume, however; it increases the nebulisation time. A fill volume 4 - 6 ml is usually recommended now. Evaporation of water produces more mist in the later part of nebulisation.

Driving gas[29,30]: Increasing the flow rate of the driving gas results in an increase in nebulised output and a reduction in particle size. A flow of 8 lit/min is recommended to optimise drug delivery. This may be problematic when a compressor is used to power the nebuliser as the flow from these is < 8 l/min, resulting in sub-optimal drug aerosolisation and delivery.

Gas density[31]: The density of gas powering the nebuliser affects the nebuliser performance considerably. It is seen in albuterol inhalation dropping considerably when nebulisation is powered with a mixture of helium and oxygen (heliox) but if its flow is increased by 50%, the delivery went up.

Steps for correct use of nebulisers

Jet nebuliser technique

1. Assemble tubing, nebuliser cup, and mouthpiece (or mask).
2. Place medicine into the nebuliser cup; use fill volume of 4 - 5 ml.
3. The patient should be seated in an upright position.
4. Connect to power source; flow of 6 - 8 l/min or compressor.
5. Breathe normally with occasional deep breaths until sputter or no more aerosol is produced.
6. Keep nebuliser vertical during treatment.
7. Rinse nebuliser with sterile or distilled water and allow to air dry.

With technology that differs from that of a traditional jet nebuliser, clinicians should thoroughly review operating instructions prior to patient use and instruction.

Cleaning the jet nebuliser (home use)

After each use:

1. Remove the tubing from the compressor and set it aside – this tubing should not be washed or rinsed.
2. Shake remaining solution from the nebuliser cup.
3. Disassemble the equipment and rinse nebuliser cup and mouthpiece with either sterile water or distilled water.
4. Shake off excess water and air dry on an absorbent towel.
5. Store the nebuliser cup in a ziplock bag.

Once or twice a week:

1. Disassemble the nebuliser and wash it in a mixture of warm soapy tap water.
2. Soak the nebuliser cup and mouthpiece for 1 hour in a solution that is one part distilled white vinegar (5%) and three parts hot water (1.25% acetic acid).
3. Discard the vinegar solution after use.
4. Rinse the nebuliser parts with sterile or distilled water.
5. Shake-off excess water.
6. Air dry on an absorbent towel.
7. Store the nebuliser in a ziplock bag.
8. Clean the surface of the compressor with a damp cloth or sponge. An alcohol or disinfectant wipe can also be used. Never put the compressor into water.

Advantages and disadvantages of inhaler devices (MDIs vs DPIs vs nebulisers).

Advantages	Disadvantages
Pressurised metered-dose inhaler (pMDI)	
1. Compact and portable	1. Difficulty in hand –mouth co-ordination
2. Drug in sealed cannister	2. Oropharyngeal deposition may be high
3. Multi-dose	3. Older device propellants may cause'cold Freon' effect and affect climate change
4. Inexpensive	4. Usually no dose counter to assess empty canister
5. Quick treatment time	5. Propellant required
6. No drug preparation required	6. CFC related problems
7. No contamination of contents	
8. Dose dose reproducilblity high	

Soft-mist inhaler (SMI)

1. Dose counter	1. Requires some co-ordination of actuation and inhalation
2. Portable and quick dose delivery	2. Slightly heavier than pMDI, DPI
3. 'Soft mist' moves slowly and low inhalation flows needed	

Dry powder inhaler (DPI)

1. Breath actuation removes need for co-ordination	1. High oropharyngeal deposition
2. Compact and portable	2. Humidity can cause drug degradation
3. Quick treatment time	3. Need adequate inhalation flow to disperse drug
4. Propellant not required	4. Patients may be intolerant to additives, e.g., lactose

Nebulisers

1. Aerosolise many drug solutions	1. Bulky, cumbersome and expensive
2. Large doses of drug can be given	2. Need for power source
3. Suitable for young, old and acutely ill patients	3. Regular cleaning and maintenance
4. Use with relaxed tidal breathing	4. Time consuming
5. Patient co-ordination not required	5. Variation in aerosol output performance between models
6. Dose modification possible	6. Wasted drug in nebuliser reservoir
7. No CFC release	7. Contamination possible
8. Can be used with supplemental oxygen	8. Not all drug solutions are available
9. Can deliver combination therapy if compatible	
10. Can be given in sick patients	

Choosing an aerosol delivery device

A choice of possible inhaler devices is dictated first by choice of drug, device availability, and any relevant reimbursement. Considerations of patient; i.e., age or ability to use the inhaler may further refine the list, for example children < 5-year-old and elderly patient should not be prescribed DPIs because they can not generate sufficient inspiratory slow. The decision of which device to choose for a particular patient is a difficult one. There are advantages and disadvantages to each type of device as has been pointed out earlier. One review of inhaler technique after training concluded that there is no difference in the ability of patient to use DPIs or MDIs. However, even with training, not all patients can use their inhaler correctly. This is true for both MDIs and DPIs. Most patients inhale too fast with an MDI and many inhale too slowly with a DPI. These findings suggest that not all patients can master the proper technique for each type of inhaler and may have natural inspiration patterns that do not match with their prescribed inhaler. It is thus better to try to match the patient's choice and predilection than to train and retrain for a particular device. There is considerable literature arguing the merits of one delivery system versus another. At the American Association for Respiratory Care sponsored consensus conference on aerosols and delivery devices, there were 3 statements that helped fuel the controversy:

1. Because the MDI and DPI delivery systems are the most convenient and provide the lowest cost dose, they should be the first choice of clinicians.
2. MDI and DPI systems are underutilised in the United States in the acute care setting. Barriers to increased use of these devices should be identified.
3. Respiratory therapists can also implement protocols to increase the conversion of nebulisers to MDI and DPI delivery systems and to reduce the misallocation of aerosol therapy.

Reviews of randomised controlled trials comparing aerosol delivery devices have shown no difference in efficacy between devices. A recent study by Direkwatanachai *et al* showed that Salbutamol administered via pMDI with Volumatic spacer or DPI (Easyhaler) are as effective as salbutamol given via a nebuliser in providing effective relief of mild-to-moderate severity acute asthma exacerbation in children between 5 and 18 years of age. A recent Indian study by Lodha *et al* also showed that Metered dose inhaler with spacer and dry powder inhaler have equal efficacy in delivering salbutamol therapy for mild-to-moderate acute exacerbations of bronchial asthma in children between 5 - 15 years of age.

Meta-analysis of randomised controlled studies have also shown that there is no evidence of superior performance in any of the inhaler devices, provided the devices were used with the correct technique. A met-analysis by Brocklebank concluded that evidence from the published clinical literature demonstrates no difference in clinical effectiveness between nebulisers and alternative inhaler devices compared to standard pMDI with or without a spacer device. An evidence-based systematic review by Dolovic *et al* concluded that each of the aerosol devices can work equally well in various clinical settings with patients who can use these devices appropriately. This was a comprehensive systematic review of pertinent randomised, controlled clinical trials (RCTs) using MEDLINE, EmBase, and the Coachrane Library databases. Only RCTs in which the same drug was administered with different devices were included. RCTs (394 trials) assessing inhaled corticosteroid, β2-agonist, and

anticholinergic agents delivered by an MDI, an MDI with a spacer/holding chamber, a nebuliser, or a DPI were identified and analysed.

Choosing a device for particular patient, therefore, depends on other considerations. A patient has to be matched to a particular device since all the devices are dependent on technique for proper use.The patient's age and educational status has to be factored in as young children may not be able to generate the airflow needed to use dry powder inhalers and may require spacer devices to be used with pMDIs. Socio-economic considerations including cost and availability also play an important role in choosing a device especially in resource-poor setting.The choice of drug and it's availability in a particular form also an important role in determining the choice.

Conclusion

Aerosolised medications can be delivered by nebuliser, metered dose inhalers or dry powder inhalers. Each of the devices have their own advantages and disadvantages and wide variety of devices available may result in confusion for the physician and the patient.Those involved in patient care must be familiar with the performance of each of these devices and the correct technique to be used with them. The device prescribed for each patient must be suited to him/her and patient instruction in correct inhaler use is of paramount importance in the management of these patients.

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CASE REPORT

JIACM 2017; 18(2): 118-20

ANCA-Negative Pauci Immune Crescentic Glomerulonephritis Presenting as Pyrexia of Unknown Origin

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Abstract

Pauci immune crescentic glomerulonephritis (CrGN) is the most common cause of rapidly progressive glomerulonephritis in adults and elderly. Most patients have circulating antineutrophilic cytoplasmic autoantibody but about 10 % of pauci immune CrGN patients are negative for ANCA. Patients of ANCA-negative pauci immune CrGN present with renal manifestations and constitutional symptoms like fever are not so frequent. We present a case of an elderly lady who was being evaluated for prolonged pyrexia and was diagnosed as ANCA-negative pauci immune CrGN.

Introduction

Pauci immune crescentic glomerulonephritis (CrGN) is the most common cause of rapidly progressive glomerulonephritis (RPGN) in adults and elderly. Most patients have circulating antineutrophilic cytoplasmic autoantibody (ANCA) but about 10% of pauci immune CrGN patients are negative for ANCA. ANCA-negative pauci immune crescentic glomerulonephritis has not been studied in detail so far and is believed to be a distinct clinical entity.

Constitutional symptoms like fever, mylagia, arthralgia and weight loss can occur in these patients. However, prolonged duration of pyrexia as the only presenting symptom of ANCA negative pauci-immune CrGN has not been documented in medical literature.

Case report

A 60-year-old housewife presented with complaints of fever for 2 months which was moderate to high grade, associated with malaise but without chills and used to subside after taking antipyretics. There were no other associated complaints like myalgia, arthralgia, rash or weight loss. She was hypertensive for last 20 years and was taking amlodipine regularly. She was evaluated at her native place for these complaints. Investigations done there showed mildly elevated blood urea and creatinine levels, mild pericardial effusion, haematuria with proteinuria, persistently elevated ESR and anaemia. Her baseline renal function tests and urine examination done 3 months back were normal. She was empirically started on anti-tubercular medications on the basis of these reports, but her fever did not subside even after a month and was referred to our institute for further evaluation. At the time of admission the patient was febrile with a temperature of 101° F, pulse rate was 96/minute regular and of normal character, blood pressure was 130/80 mmHg in both arms in supine position, mild pallor was present and there was no pedal oedema, lymphadenopathy or rash. Systemic examination was essentially normal.

Haemoglobin was 7.1 gm%, TLC - 9,400/cumm, MCV - 63.7fl/cell, MCH - 22.6 pg/cell, MCHC - 35.5%, and reticulocyte count - 2%. Peripheral smear showed microcytic hypochromic anaemia with target cells. Vitamin B12 and folate levels were normal. Total iron was 30 mcg/dl with a saturation of 14.6%. Serum ferritin level was low. Guaiac test of stool for occult blood was negative twice. ESR was 98 mm/hr.

Renal function tests were deranged with urea of 54 mg/dl, creatinine - 1.5 mg/dl and uric acid - 9.1 mg/dl. Serum total protein was 6 gm/dl with albumin of 2.3 gm/dl and globulin of 3.7 gm/dl. Liver function tests, lipid profile and serum electrolytes were normal. Urine examination revealed 6 - 8 RBC/hpf, 2 - 4 pus cells/hpf and 3+ albuminuria with occasional granular casts. Urine for dysmorphic RBCs was positive. Urinary spot ACR (albumin/creatinine ratio) was 2,162 mg/g. Urine culture was sterile. Urine cytology did not show any malignant cells in three consecutive samples. Three samples of urine were negative for acid fast bacilli.

Bone marrow examination was suggestive of reactive changes with no granulomas, hemoparasites or atypical cells. *Mycobacterium tuberculosis* PCR was negative in bone marrow. Bone marrow culture was sterile. HIV, HBsAg, anti-HCV and VDRL were non reactive. Serum electrophoresis did not show any M-band. Thyroid profile was normal and mantoux test was negative.

ANA, anti-ds DNA, anti Smith, cANCA and pANCA were negative. ANA was done by immunofluorescence (IF) technique, cANCA and pANCA were done by both enzyme

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immunoassay (EIA) and IF methods. Complements levels and immunoglobulin levels were normal. Ultrasound abdomen was normal. Chest X-ray and ECG were normal.

2D echocardiography showed mild left ventricular hypertrophy, ejection fraction of 55% and mild pericardial effusion with no clots or vegetations.

As the investigations did not lead to any conclusion and patient's fever was persisting a renal biopsy was done on day 7 of her hospital stay in view of persistently deranged renal function tests, hematuria, albuminuria and raised ESR. Renal biopsy report showed focal necrotising and crescentic glomerulonephritis, featuring segmental tuft necrosis in 22.2% glomeruli and crescents in 61.1% of sampled glomeruli (4 cellular, 4 fibrocellular and 3 fibrous crescents) (Fig. 1).

Several glomeruli showed secondary segmental tuft sclerosis in relation to proliferating extracapillary cells and viable glomeruli revealed a non-proliferative morphology.

Immunofluorescence studies did not show significant glomerular immune complex deposits.

Patchy acute tubular injury involving viable cortical tubules and multifocal severe interstitial nephritis were observed in sampled cortical parenchyma (Fig. 2). All these findings were suggestive of pauci-immune focal necrotising and crescentic glomerulonephritis. Birmingham vasculitis activity score was 20 in our patient.

She was started on oral prednisolone 1 mg/kg daily and oral cyclophosphamide 2 mg/kg daily. Low dose of enalapril (2.5 mg) twice daily was added for hypertension. Her fever subsided within two days of starting the medication and was discharged on these medications. Steroid was tapered after 6 weeks and cyclophosphamide was continued. In the 3rd month of treatment her blood urea and creatinine

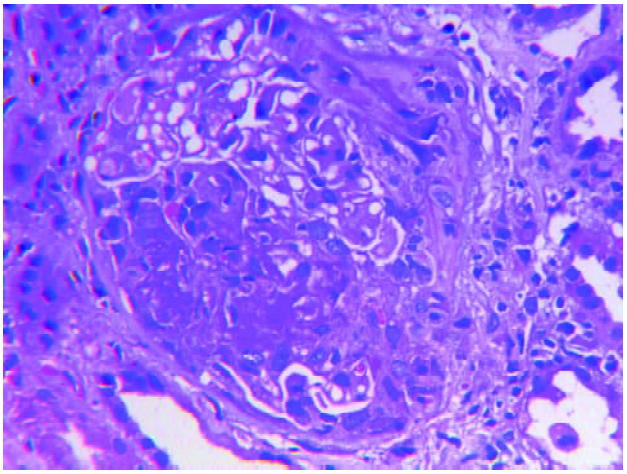

Fig. 1: *Renal biopsy showing crescentic glomerulonephritis with segmental tuft necrosis.*

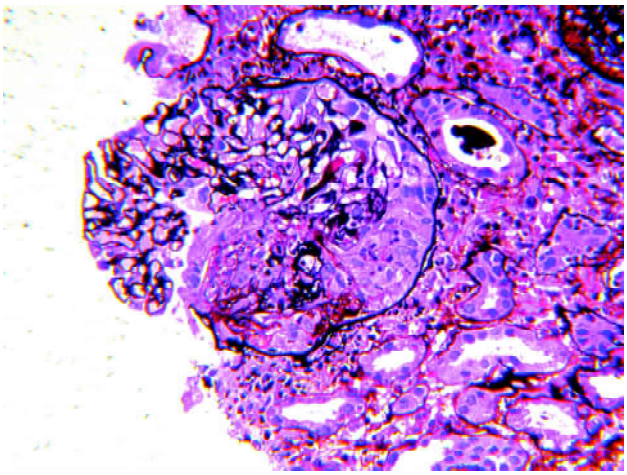

Fig. 2: *A glomerulus with crescent formation and tubules showing evidence of tubular injury.*

levels became normal, urine examination was negative for hematuria and dysmorphic RBC's but mild proteinuria persisted. She remained afebrile during treatment. Cyclophosphamide was stopped after complete remission and low dose steroid with oral mycophenolate 1 gm twice daily was started as a part of maintenance regime. Repeat ANCA was negative during follow-up period. A repeat 2D echocardiography, done after 3 months did not show any pericardial effusion.

Discussion

Crescentic glomerulonephritis (CrGN) is characterised by rapidly deteriorating renal functions associated with oliguria, hematuria and proteinuria which leads to renal failure if not promptly diagnosed and treated. CrGN is classified into three categories based on immunological features. Type 1 has circulating anti glomerular basement membrane antibody associated with linear deposit of IgG on glomerular basement membrane, type 2 is characterised by immune complex deposition in glomeruli and is the most common cause of RPGN in children and type 3 pauci immune crescentic glomerulonephritis is characterised by focal necrotising crescentic glomerulonephritis and is the most common cause of RPGN in adults and elderly[1].

Most of the patients of pauci immune crescentic glomerulonephritis have systemic small vessel vasculitis like Granulomatosis with Polyangiitis, Microscopic Polyangiitis, Eosinophilic Granulomatosis with Polyonglitis or Renal Limited Vasculitis[2]. 80 - 90% of these patients have circulating ANCA (anti neutrophilic cytoplasmic autoantibody)[3]. ANCA is believed to play a role in pathogenesis of CrGN[4]. However, about 10 % patient's of pauci immune CrGN are negative for ANCA and this variant has not been studied in detail except for few available case

series[5]. It is thought that ANCA-negative pauci immune CrGN might be a different clinical entity from ANCA-positive pauci immune CrGN and neutrophils are implicated in pathogenesis of this disease variant[5].

ANCA-negative pauci immune CrGN presents at an average age of 40 years whereas the usual age of presentation is 58 years in ANCA-positive patients[6]. ANCA-negative patients have less extra renal and constitutional symptoms (fever, weight loss and myalgia) as compared to ANCA-positive pauci immune CrGN[6]. In the study done by Chen *et al*, fever was present in only 21% of ANCA-negative pauci immune CrGN patients whereas it was significantly higher (66.7%) in ANCA-positive patients. In the same study it was shown that ANCA-negative CrGN is associated with a greater degree of proteinuria, nephrotic syndrome and glomerular lesions than ANCA-positive patients[6]. Interstitial fibrosis and glomerulosclerosis are also more common in ANCA-negative pauci immune CrGN[7].

Our patient was an elderly lady and fever was the only presenting symptom, which is unusual, and has not been reported in medical literature. There are no treatment guidelines for ANCA-negative pauci immune CrGN and treatment is usually based on ANCA positive CrGN protocols. Overall, ANCA-negative pauci immune CrGN has poor prognosis as compared to ANCA-positive pauci immune CrGN[6].

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"How can he practice true compassion
Who eats the flesh of an animal to fatten his own flesh?
Riches cannot be found in the hands of the thriftless,
Nor can compassion be found in the hearts of those who eat meat."

– THIRUKURAL 251-252.

CASE REPORT

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Non-HFE Hereditary Haemochromatosis Presenting as Hepatic Encephalopathy

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Abstract

Hereditary haemochromatosis is a heterogeneous genetic disorder inherited as an autosomal recessive trait. We describe a case of a 52-year-old male who presented with clinical features of hepatic encephalopathy and was found to have cirrhosis of liver, hyperpigmentation, diabetes mellitus and hypogonadism. Laboratory investigation revealed evidence of haemochromatosis based on iron studies and liver biopsy with absent HFE mutation.

Introduction

Hereditary haemochromatosis is an iron overload state with enhanced intestinal absorption of iron, leading to organ damage. This is the most common inherited liver disease and also the most common autosomal recessive genetic disorder. Two mutations in the HFE gene have been described, C282Y and H63D. C282Y homozygosity or compound heterozygosity C282Y/H63D is found in most patients with hereditary haemochromatosis. The term "non-HFE haemochromatosis" refers to several phenotypically similar but genetically distinct forms of hereditary haemochromatosis affecting individuals without pathogenic mutations of HFE. The involved genes are transferrin receptor 2 (TfR2), hemojuvelin (HJV), and hepcidin (HAMP). Early recognition of haemochromatosis is essential for preventing destructive organ damage.

Case report

A 52-year-old male (chronic smoker and alcoholic) presented to medical emergency with altered level of consciousness and history of a similar episode 20 days before admission. Patient was diagnosed type 2 diabetes mellitus two years back for which he was initially on oral hypoglycaemic drugs and later switched to insulin. He had history of loss of body hair (chest, abdomen, back and pubic area) and loss of libido with enlargement of breast tissue for last 2 years, lethargy for one and half years. Increased pigmentation of skin which predominantly involved face, neck, extensor aspect of forearms and dorsum of hands and legs appeared simultaneously, progressed gradually over time and was associated with persistent yellowish discolouration of sclera and urine which had not progressed over time and was still seen at the time of presentation. Shortness of breath (NYHA class 2) had also been present for same duration. Patient was also having abdominal distention and pedal oedema of pitting type for 6 months.

No history of fever, cough/expectoration, chest pain, clay coloured stools, chronic diarrhoea, pruritus, bleeding from any site, decreased urine output, numbness of limbs, diminution of vision, arthralgia, blood transfusions, iron and ascorbic acid ingestion could be elicited.

On examination, patient had a pulse rate of 84/min, regular and BP of 114/82 mmHg in right arm in supine position. He had icterus and pedal oedema of pitting type. Patient had a height of 165 cm and weight of 102 kg with BMI of 37.47 kg/m^2. He had scanty hair over body, gynaecomastia (Fig. 2), acanthosis nigricans, grayish black pigmentation over face (Fig. 1), nape of the neck, dorsal aspect of bilateral hands,

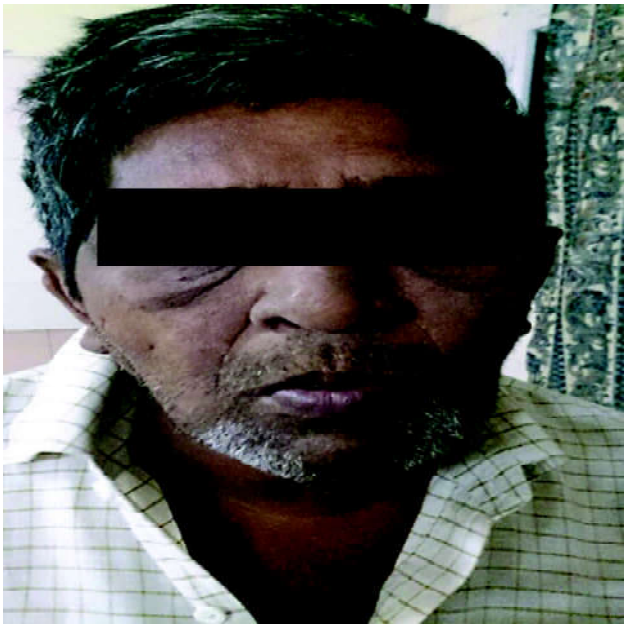

Fig. 1: *Hyperpigmentation of face.*

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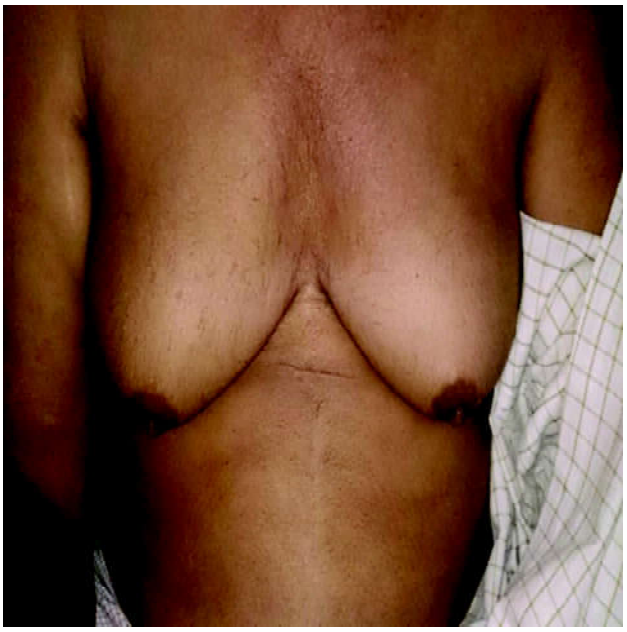

Fig. 2: *Gynaecomastia with loss of hair over chest and abdomen.*

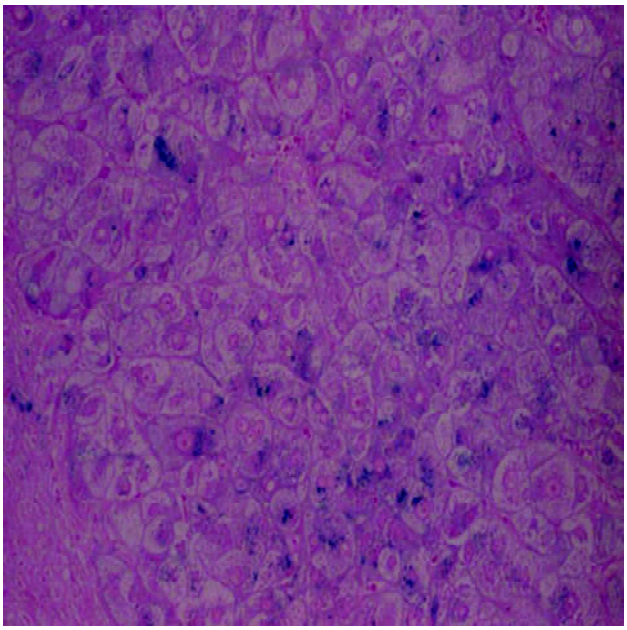

Fig. 3: *Histopathological slide of liver tissue showing cirrhosis with intrahepatocytic iron deposition.*

forearms and dorsum of bilateral feet with both testes placed normally in the scrotum.

Systemic examination of respiratory and cardiovascular systems did not reveal any abnormality. Abdominal examination revealed distended abdomen with full flanks without any organomegaly. Shifting dullness was present. CNS examination showed a confused patient with presence of flapping tremors. Family history of diabetes mellitus was present in patient's youngest brother and his wife.

On laboratory investigation complete haemogram revealed haemoglobin 11.0 gm/dl (13.3 - 16.2 gm/dl), blood sugar - 288 mg%. SGOT/PT - 64/41 U/L (< 40 U/L), serum alkaline phosphatase - 128 U/L (39 - 117 U/L), serum proteins - 5.6 g/dl (6.7 - 8.6 g/dl). INR of 2.88. Urine complete examination showed sugar - 2+. Iron studies showed plasma iron - 153 µmol/l (50 - 150 µmol/l), total iron binding capacity - 196 µgm/dl (250 - 370 µgm/dl), transferrin saturation - 78.06% (22 - 46%), serum ferritin - 1,011 µg/l (20 - 250 µg/l), fT4 - 12.6 pmol/l (9.0 - 16 pmol/l), fT3 - 4.2 pmol/l (3.7 - 6.5 pmol/l) with TSH levels of 2.2 mIu/l (0.34 - 4.25 mIu/l). His LH - 2.68 U/L (2.0 - 12.0 U/L), FSH - 0.69 IU/L (1.0-12.0 IU/L) and testosterone - 4.24 nmol/l (9.36 - 37.10 nmol/l) levels were within normal range. HIV/HBsAg/anti HCV were negative. AFP (alpha feto protein) - 4.33 IU/ml (0.0 - 5.8 IU/ml). Urine for microalbumin was 22.7 µg/mg of creatinine, HbA1C - 7.8%, upper gastrointestinal endoscopy showed low grade esophageal varices, osteopenia was found on dexa scan. ECG was normal. Fundus was normal. Ultrasound abdomen revealed free fluid , liver measured 12 cms with slightly altered echotexture with portal vein diameter of 11.5 mm at porta. Radiograph of the chest, hands, feet, elbows and knees did not show any abnormality. Echocardiography showed MVP with mild MR, E > A with LVEF 56%. NCCT head and MRI brain was within normal limits. Liver biopsy showed evidence of cirrhosis with intrahepatocytic iron deposition and histologic scoring for liver iron was 4+ (masses visible at low power, 10×) (Fig. 3). HFE gene mutations (C282Y and H63D mutations) were negative.

In this case, presence of diabetes, stigmata of chronic liver disease, hyperpigmentation, secondary hypogonadism, features of iron overload (iron study and liver iron staining grade-4) with absent HFE mutation suggested the diagnosis of non-HFE heriditary haemochromatosis. Patient was put on tab deferasirox 500 mg qid, tab rifaximin 550 mg bd, inj insulin mixtard (30/70) 20 U and 16 U subcutaneously half hour before breakfast and dinner respectively. Phlebotomy could not be done in this patient because of anaemia (Hb 11 gm%). Patient improved clinically with serum ferritin and transferrin saturation after 4 weeks of therapy was 226 µg/l and 54.8% with blood sugar in target range.

Discussion

Haemochromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity. This is the most common inherited liver disease and the most common autosomal recessive genetic disorder. Two mutations in the HFE gene have been described. The first, C282Y, comprises the substitution of tyrosine for cysteine at amino acid position 282. In the second, H63D, aspartic acid is substituted for histidine in position 63. HFE-associated

HH (HFE-HH) or type 1 HH is the most common form, especially in populations of Northern European origin, where the C282Y mutation has a high allele frequency.

Haemochromatosis that is unrelated to mutations in the HFE gene are collectively referred to as non-HFE haemochromatosis. Non-HFE haemochromatosis makes up a larger proportion of HH cases in areas where the C282Y mutation is less common, such as Southern Europe and Asia and are rare and genetically heterogeneous[1]. Non-HFE HH can be further differentiated according to the gene mutated. There are four main types of non-HFE HH. The molecules mutated in all forms of HH are related in pathways involved in the regulation of iron homeostasis. Hepcidin, the central regulator of iron homeostasis, and hemojuvelin are mutated in juvenile or type 2 HH. Transferrin receptor 2 is mutated in type 3 HH and the iron exporter ferroportin is mutated in the autosomal dominant type 4 HH, or ferroportin disease.

The diagnosis of non-HFE-haemochromatosis requires sequential steps. The first diagnostic step is to suspect that primary iron loading is present, as in HFE-related haemochromatosis. This is frequently based on the findings of abnormal transferrin saturation (TS), usually > 45% in both sexes and/or increased serum ferritin (SF) (> 200 μg/l in adult females and > 300 μg/l in adult males). More rarely, the suspicion derives from clinical symptoms related to iron-induced organ failure or from complications in the presence of abnormally high iron parameters. The following step is to exclude mutations in the HFE gene or non HFE mutations.

If the diagnosis of HFE haemochromatosis is not confirmed by finding a susceptible HFE genotype, it is advisable to demonstrate increased total body iron, before starting expensive and time-consuming search for mutations in other genes. Liver iron concentration (LIC) is considered a measure of total body iron and liver biopsy remains the gold standard for defining LIC[2].

Early diagnosis and therapeutic phlebotomy to maintain low normal body stores is crucial and can prevent all known complications of haemochromatosis. If untreated, haemochromatosis may lead to death from cirrhosis, diabetes, malignant hepatoma, or cardiac disease[3]. The interval between procedures is determined by the level of ferritin, which should be lower than 50 mcg/ml[4]. Deferasirox is the oral iron chelator used as an adjunct to phlebotomies or instead of phlebotomy in patients in whom these procedures are poorly tolerated.

Conclusion

Haemochromatosis is a genetic disorder of iron metabolism which can rarely be caused by non-HFE mutations. Early detection and treatment of this disorder, by life long phlebotomy or chelation therapy, can guarentee a normal lifespan.

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"Folks, I'm telling you,
birthing is hard
and dying is mean –
so get yourself a little loving in between."

– Langston Hughes.

CASE REPORT

JIACM 2017; 18(2): 124-25

Acute Isoniazid Poisoning: A Case of Lethal Dose Intake

Mridul Chaturvedi, Anjana Pandey**, Vinisha Chandra***, Rosmy Jose****

Abstract

We present a case of intentional overdose of Isoniazid (INH) in a 17-year-old female who was recently started on anti-tubercular drugs CAT I and presented to us with repetitive seizures not responding to treatment. Physician awareness and prompt treatment in such drug related toxicity is important to rescue a life even when laboratory investigations are not available at hand. We are reporting this case to emphasize the importance of good clinical acumen even in a resource poor setup for treating INH toxicity.

Keywords: Isoniazid, acute toxicity, neurological symptoms.

Introduction

Isoniazid is widely used in the treatment of all forms of tuberculosis. Acute Isoniazid poisoning is uncommon in India. Doses of 35 to 40 mg/kg have resulted in seizures. Doses of 80 to 150 mg/kg will produce seizures and may cause death. Acute ingestion of 2 to 3 gms in an adult is potentially toxic, while 10 to 15 gms is frequently associated with death, if untreated. Isoniazid overdose causes seizures, generally within 1 hour post-ingestion but may occur from 30 mins to 5 hours following ingestion. As little as 1.5 gms of isoniazid ingested acutely may cause toxicity in an adult.

Case report

A 17-year-old girl was on isoniazid (300 mg) CAT I for pulmonary tuberculosis from February 2016. She was referred to emergency department with history of intentionally consuming more than 20 pills of Isoniazid (300 mg each) 1.5 hours prior to admission. Within an hour of consumption, she developed 2 - 3 episodes of vomiting followed by generalised tonic clonic convulsions. The possibility of consumption of a toxic substance with suicidal intent was confirmed by her relatives. Patient had one episode of GTCS in the emergency. On examination, she was afebrile with pulse of 118/min, regular and good volume. BP was 100/80 mm of Hg, respiratory rate was 32/min and respiration was acidotic. In post-ictal phase, she was comatose moving all four extremities equally on deep painful stimulus.There was no sign of 'meningeal irritation, tone was normal, and reflexes were brisk with bilateral flexor plantar response. Respiratory system examination revealed bilateral conducted sounds and no added sounds. Cardiovascular system examination revealed normal heart sounds heard with no appreciable murmur. On abdominal examination, it was soft, non tender, with no apparent organomegaly.

As facility for arterial blood gas estimation was not available, she was empirically started on intravenous bicarbonate on the basis of clinical evaluation. Injection mannitol and loading dose of phenytoin were given. Acidosis persisted so she was empirically started on pyridoxine 5 gms through Ryle's tube as intravenous pyridoxine was not available. She had no further convulsions and acidosis responded clinically within 24 hours although arterial blood gas analysis was not performed. Levels of INH in blood and urine could not be measured due to lack of facilities. Her investigations revealed Hb 9 g/dl Tlc 13,400 c/mm3 on day 1 and other biochemical investigations were normal (Na - 138 meq/l K - 3.8 meq/l Ca 1.18 meq/l blood sugar 98 mg/dl). Her serial follow-up of liver function and kidney function tests was as follows:

Day	SGOT (U/L)	SGPT (U/L)	S. creat (mg/dl)	B. urea (mg/dl)
Day 1	23	17	0.7	18.8
Day 2	250	250	0.4	36.6
Day 3	250	250	0.7	27.9
Day 4	27	21	0.9	30

Biochemical profile of liver function and kidney function tests of the patient.

On day 1, the liver profile of the patient was normal however along with clinical deterioration liver fuction tests became deranged over a period of three days.With clinical improvement, liver function tests normalised on day 4.There was no derangement in renal profile throughout the course of hospital stay.

On the 5th day, patient started showing clinical improvement and was kept under observation for another three days. The patient is on regular follow-up and is on

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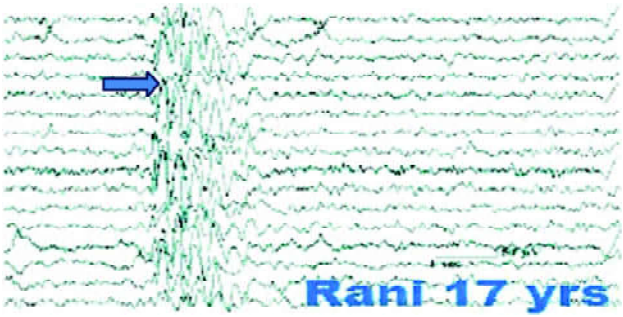

Fig. 1: *EEG of the patient of INH toxicity (arrow shows epileptiform discharge).*

continuation phase of ATT and has been seizure free since then.

Discussion

After acute ingestion of high doses (5 - 6 gms) of isoniazid, toxicity appears within ½ to 3 hours. Doses of 35 to 40 mg/kg have resulted in seizures and amounts greater than 80 to 150 mg per kg can lead to death[1]. Such mode of ingestion is usually suicidal[2]. Manifestations of acute intoxication are acidosis, coma and tonic-clonic-seizures[3]. Isoniazid toxicity may be interpreted in terms of effects on pyridoxine metabolism. Isoniazid binds to pyridoxal 52-phosphate to form isoniazid-pyridoxalhydrazones. They deplete neuronal pyridoxal 52-phosphate. Thus decreasing levels of the inhibitory neurotransmitter GABA. Decreased levels of GABA lead to cerebral overexcitability[4] and lowered seizure threshold. The antidote is replenishment of pyridoxine.

The present case is unique because, even after intake of fatal dose, recovery was complete due to timely diagnosis and intervention unlike other case reports (Prabhakaran *et al*)[5] where outcome was fatal. The lack of laboratory facility to evaluate INH levels , ABG and nonavailability of parenteral preparation of pyridoxine should not stop us from treating the patient. A physician's clinical understanding takes upper hand in such situations. In case of isoniazid toxicity, pyridoxine should be administered in a dose equivalent to the suspected amount of isoniazid ingested. If amount is unknown, 5 gms of pyridoxine should be given. Haemodialysis should be considered if the condition of the patient does not improve. Our case illustrates that even lethal dose toxicity can be reversed with intensive care and awareness about INH toxicity.

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"Karma, memory, and desire are just the software of the soul.
It's conditioning that the soul undergoes
in order to create experience.
And it's a cycle.
In most people, the cycle is a conditioned response.
They do the same things over and over again."

– Dr. Deepak Chopra.

CASE REPORT

JIACM 2017; 18(2): 126-28

Distal Symmetrical Polyneuropathy: A Rare Presentation of the Churg Strauss Syndrome

Peeyush Kumar,Richa Dewan**, Vanlalmalsawmdawngliana*, Sumeet Singla***, S Anuradha*****

Abstract

Churg Strauss syndrome is a relatively uncommon form of small vessel vasculitis. It is predominantly characterised by the presence of pulmonary involvement, hypereosinophilia, asthma and sinusitis. We describe the case of a 23-year-old woman who presented with bilateral, distal, symmetrical sensori-motor polyneuropathy: a rare presenting manifestation.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a multi-systemic disorder, categorised as a small vessel anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs). Formerly known as "Churg-Strauss syndrome," this eponym has been replaced during the 2012 Revised International Chapel Hill consensus conference (CHCC), with the aim of focusing on the histopathology of the disease[1]. Churg-Strauss syndrome (CSS) is a systemic disorder characterised by asthma, hypereosinophilia, and systemic vasculitis and frequently involves peripheral nerves and skin.

According to the 1994 CHCC, EGPA is defined as an eosinophil-rich and granulomatous inflammation often involving the respiratory tract, and necrotising vasculitis predominantly affecting small to medium-sized vessels, associated with asthma and eosinophilia. Untreated, CSS may be fatal and up to 50% die within three months of the onset of vasculitis but early diagnosis and treatment promises an excellent clinical response[2].

Case report

A 23-year-old woman, diagnosed with bronchial asthma for 2 years, presented with numbness and tingling in the distal parts of all four limbs for 1 month and progressive weakness in distal parts of both lower and upper limbs for 1 month. The patient developed numbness and tingling in both lower limbs 1 month ago which was gradually progressive followed by involvement of hands in a glove and stocking distribution. There was a history of slippage of footwear followed later by difficulty in standing and walking over a period of 1 month. Weakness in gripping and holding objects ensued. The lower limbs were weaker than the upper limbs.

There was a history of rash for 1 month. The rash was insidious in onset, maculo papular, non-itchy, reddish, non tender which gradually progressed to involve bilateral thighs and shins. There was no bladder/bowel/cranial nerve involvement. There was no fever, arthritis , arthralgia, oral ulcers, photosensitivity, or raynaud's phenomenon. There was no history of drug intake or toxin exposure.

Examination revealed a pulse rate of 82/minute, BP - 110/70 mmHg and respiratory rate of 22/minute and she had mild pallor. Respiratory examination revealed bilateral expiratory wheeze. Nervous system examination revealed bilateral symmetrical, distal muscle weakness with absent deep tendon reflexes (supinator and ankle jerk). The bilateral plantar response was flexor. There was a bilateral sensory loss to touch, pain, temperature in glove and stocking distribution. She had a high stepping gait.

Investigations revealed haemoglobin 12.2 gm/dl, total leukocyte count 18,800 cells/mm^3, (neutrophils 46%, lymphocytes12% and eosinophils 36%) platelet count 2.2 lakhs/mm^3. The absolute eosinophil count was 5,846 cells/mm^3. ECG showed left axis deviation with low voltage complexes. Urine examination was unremarkable. The X-ray chest was normal and the X-ray PNS showed left maxillary sinusitis. Creatinine phosphokinase was 507 U/L. The rest of the biochemical profile was within normal limits.

The nerve conduction study was suggestive of mixed axonal/demyelinating sensorimotor polyneuropathy. On pulmonary function testing-FEV1/FVC: 68% predicted normal, and post-bronchodilator FEV1:13% increment was documented, consistent with reversible obstructive airway disease.

The nerve biopsy from the sural nerve revealed necrotising vasculitis with eosinophilic infiltration, secondary demyelination and loss of large myelinated fibres (Fig. 1 - 2). A Skin biopsy demonstrated infiltration of eosinophilic cells surrounding the blood vessels. The CECT thorax

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demonstrated multiple patches of consolidation in left upper lobe, with patches of ground glass opacities in right lower lung, lingular segment and basal area of left lower lobe. Bilateral bronchial wall thickening and interlobular septal thickening suggestive of bronchiolitis was seen. The ANCA, ANA, RA factor were negative.

The five factor score of patient was 0, so she was started of oral prednisolone 50 mg daily. She responded to the treatment and improved symptomatically. She was discharged and was kept under follow-up. Two weeks later she developed an episode of acute shortness of breath. A 2D echo at this time demonstrated dilated cardiomyopathy, moderate pericardial effusion with severe left ventricular systolic dysfunction: left ventricular ejection fraction 20%. At this point in her clinical course, her FFS was 1 and she was started on oral prednisone at dosage of 1 mg/kg/day and intravenous cyclophosphamide pulse 15 mg/kg of body weight, following which she showed significant improvement. She had received 3 cycles of cyclophosphamide and is under follow-up.

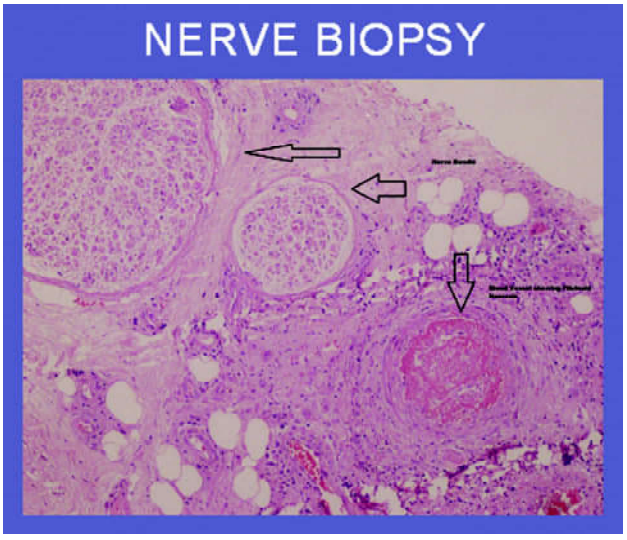

Fig. 1: *Blood vessels showing fibrinoid necrosis.*

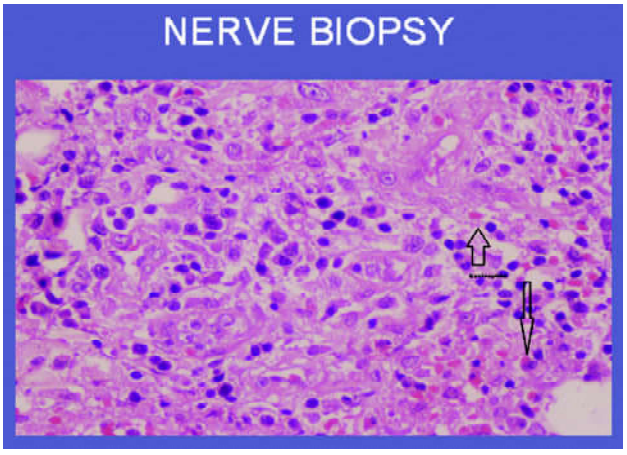

Fig. 2: *Showing tissue infiltration by eosinophils.*

Discussion

The ACR 1990 requires the presence of any four or more of the six criteria (asthma, eosinophilia > 10%, neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities, extravascular eosinophils) for a diagnosis of Churg Strauss syndrome. Our patient fulfilled the ACR 1990 diagnostic criteria of Churg-Strauss syndrome with asthma, eosinophilia, sinusitis and vasculitis involving the peripheral nerves supported by characteristic sural nerve biopsy findings. It has a sensitivity of 85% and a specificity of 99.7%[2]. Neurological manifestations of Churg-Strauss syndrome are common and usually consist of acute or subacute multiplex mononeuropathy. Peripheral polyneuropathy as observed in this patient, is extremely rare. Approximately 48% of patients with EGPA have circulating antibodies, usually anti-myeloperoxidase. Anti-myeloperoxidase antibodies appear to determine the subgroup of patients with a higher frequency of renal damage, alveolar haemorrhage, and central nervous system damage. ANCA negative patients have higher frequency of cardiac involvement. The present patient was ANCA negative. The five factor score (FFS) guides clinicians for management and assessing prognosis of patients. This score assigns one point to each of the following items: gastrointestinal involvement/CNS involvement/cardiac involvement/proteinuria > 1 g/24 hour and serum creatinine > 141 mmol/l[3]. Patients with poor prognostic factors (FFS-1) are often treated with both glucocorticoids (classically prednisolone at dosage of 1 mg/kg of total body weight/day with a maximum dosage of 75 mg/day, for 1 month and then tapered) and cyclophosphamide (2 mg/kg of total body weight/day), while the typical approach for patients with a better prognosis (e.g., FFS of 0) is glucocorticoid therapy alone[4]. Recently, a revised FFS has been proposed; an age over 65 years/cardiac symptoms/gastrointestinal involvement/renal insufficiency (serum creatinine > 150 mmol/l) and absence of ear, nose, and throat manifestations have been pointed out as predictors of 5-year mortality[5]. The reported frequency of cardiac involvement varies widely (16% - 92%), accounting for approximately one-half of the deaths attributable to Churg-Strauss syndrome[6,7].

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"The sage creates music to correlate with Heaven and creates rituals to correlate with Earth. When rituals and music are well established, we have Heaven and Earth functioning in perfect order."

– CONFUCIUS.

CASE REPORT

JIACM 2017; 18(2): 129-32

A Case of Psoriatic Spondyloarthropathy Presenting as Unilateral Sternoclavicular Joint Arthritis

BMS Lamba, Arvind Kumar**, Arpita Dash***, Manohar**, Abhishek Mittal**, Pulin Kumar Gupta*****

Abstract

Sternoclavicular joint is not commonly involved in inflammatory arthritis and is more often associated with septic or infective focus. It is also very frequently overlooked by physicians and rheumatologists. We hereby report a case of unilateral sternoclavicular joint arthritis treated before as tubercular and gouty arthritis. It later turned out to be a case of psoriatic arthritis and that too without any dermatological involvement.

Keywords: SC (sternoclavicular), SpA (spondyloarthropathy), MCP (metacarpophalangeal joint), DIP (distal interphalangeal joint).

Introduction

Psoriatric arthritis is a seronegative spondyloarthropathy characterised by typical skin involvement along with spondyloarthropathy, dactylitis, and DIP joint involvement. Normally, skin changes in psoriasis precade arthritis by an average of 8 - 10 years in 70% of patients but rarely, arthritis precedes, or in 30% cases may occur simultaneously. 95% of patients with psoriatic arthritis have peripheral joint disease (synovitis, tenosynovitis, dactylitis, and enthesitis). In 5% cases, axial spine involvement is seen and sacroiliitis is typically asymmetric as compared to ankylosing spondylitis or IBD-associated spondyloarthropathy. We hereby report a rare case of psoriatic spondyloarthropathy where sternoclavicular joint (axial) arthritis was the presenting complaint and, that too, without skin involvement.

Case

A 24-year-old gentleman, resident of Begusarai, Bihar, working as a daily wage worker presented to us with chief complaints of pain and swelling of right sternoclavicular joint for three months, low backache, and pain and swelling of right middle finger and right 2nd, 3rd, 4th toes for last 1½ months. There was no history of fever, trauma, early morning stiffness, throat infection, rashes, photosensitivity, oral or penile ulcers. There was no past or family history of connective tissue disorder. He was a smoker and occasional alcoholic. He had shown to many physicians and rheumatologists and MRI of right sternoclavicular joint was done and which suggestive of osseous oedema with irregular margin, minimal fluid, generalised swelling and inflammation (left SC joint was normal). Joint aspiration revealed a cell count of 2,000 cells/ml with no evidence of AFB, urate crystals or septic arthritis. Gene expert test of joint fluid was negative for AFB. A provisional diagnosis of tubercular arthritis was made and he was started on ATT but there was no relief and after 15 days he developed pain and swelling of right middle finger alongwith swelling of right 2nd, 3rd, 4th toes. He was again evaluated and based on high uric acid levels (8.5 mg%), he was started on allopurinol 100 mg thrice a day along with NSAIDs, but he remained symptomatic and the swelling and tenderness of right sternoclavicular joint and right middle finger increased. He continued ATT and treatment for gout for 1½ months but to no relief. So, he came to RML hospital for a second opinion.

At the time of presentation, his general physical examination and vitals were stable. The right sternoclavicular joint was swollen, but non-tender. The left sternoclavicular joint was normal (Fig. 1).

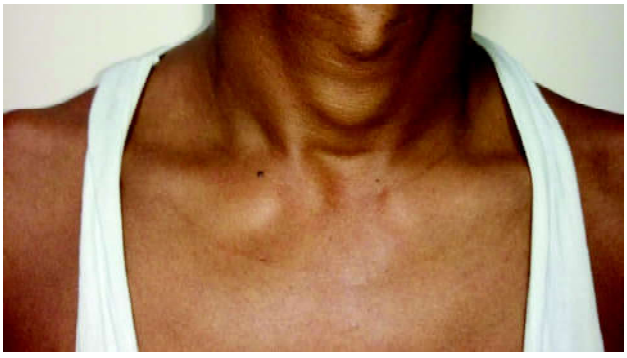

Fig. 1:

Hand examination revealed swollen and minimally tender right middle finger from tip to MCP joint. Distal

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interphalangeal joint was typically tender and swollen as compared to proximal inter phalangeal joint alongwith soft tissue swelling (Fig. 2).

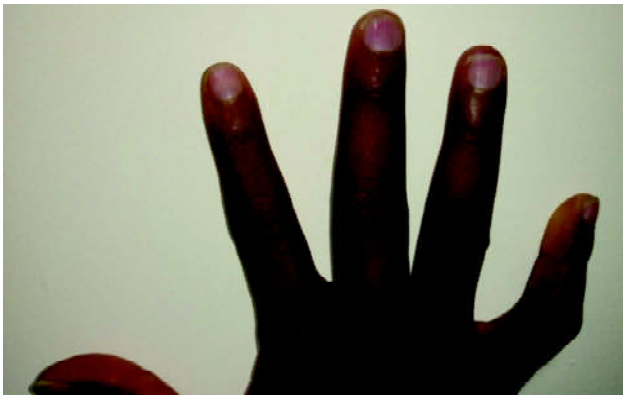


Fig. 2:

Similarly, his foot examination revealed tender and swollen right 2nd till 4th toes where the soft tissue swelling was conspicuous as compared to synovitis (Fig. 3).

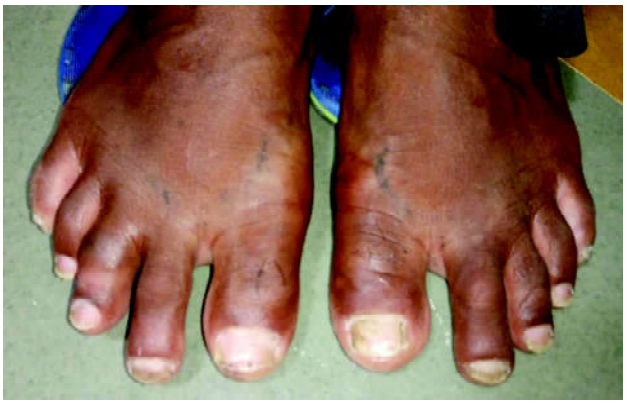


Fig. 3:

Nail examination was grossly normal, so we sent the patient to dermatologist for re-examination with dermoscopy which revealed pitting with onycholysis of bilateral toes and right 2nd/3rd finger.

On detailed questioning, he gave history of off and on low backache that was present throughout the day with no diurnal variation and no early morning stiffness.

His modified Schober's test was negative. He had mild enthesitis of tendoachilles tendon of right side. Otherwise, his respiratory, cardiac and abdomen examination was normal.

Skin examination did not reveal any abnormality or any evidence of psoriatic skin changes. Relevant investigations were normal except for mildly raised ESR and CRP. HIV-1 and 2, HbsAg, anti HCV, mantoux test and quantiferon TB gold test were also negative.

Autoimmune profile – ANA by IFA method, HLA B27, anti CCP and rheumatoid factor were negative. His X-ray pelvic showed bilateral sacroiliac joint involvement with grade-2 sacroiliitis (right > left) (Fig. 4).

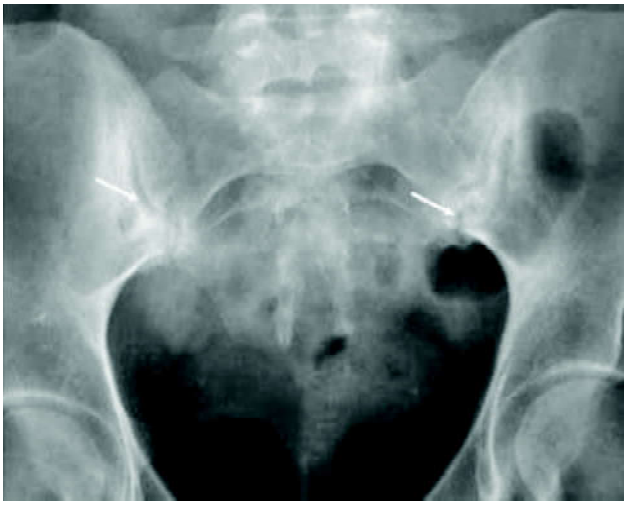


Fig. 4:

MRI of sacroiliac joint revealed bilateral sacroiliitis (right > left) with osseous edema on iliac as well as sacral sides of the joint and articular erosions alongwith increase joint space fluid. Hence, a diagnosis of seronegative psoriatic spondyloarthropathy, with axial involvement was made.

He was started on methotrexate, sulfasalazine, folic acid and NSAIDs alongwith depot intramuscular methylprednisolone injections.

His ATT and allopurinol were stopped. After the treatment patient reported dramatic improvement in his symptoms and became asymptomatic within two weeks. His sternoclavicular joint swelling and pain decreased substantially as also in his hand and toe joints. His uric acid has also normalised. He started doing all his daily activities with ease and has been advised to follow-up in our rheumatology and dermatology clinics, regularly with haemogram and liver function test reports.

Discussion

Psoriatic arthritis is a seronegative inflammatory joint disease and occurs, on an average, in 26% of patients with psoriasis. Seronegative arthritis, means that the rheumatoid factor should be negative. However, low titre rheumatoid factor can be detected in 5% to 9% of patients and anti CCP antibodies in 5% of psoriatic arthritis patients[1]. This it may be misdiagnosed as rheumatoid arthritis. However, the presence of DIP joint involvement, enthesitis, and dactylitis

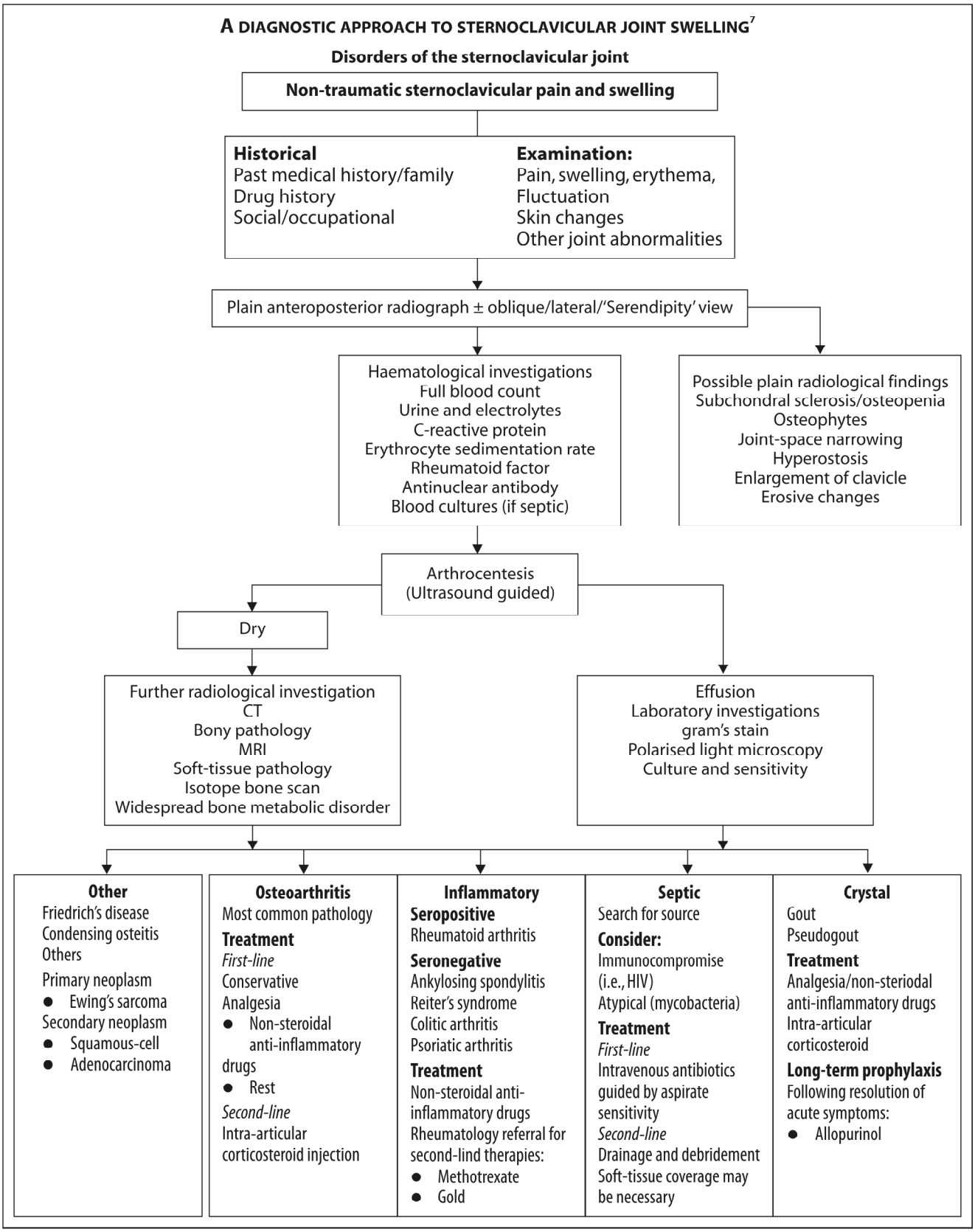


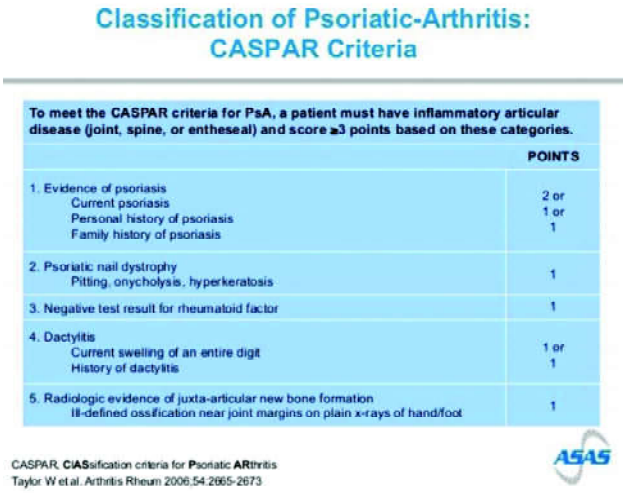
Fig. 6: *Diagram giving the diagnostic protocol for the investigation of non-traumatic steroclavicular pain and swelling.*

supports a diagnosis of psoriatic arthritis regardless of the serologies. As in other inflammatory diseases, ESR, CRP and anaemia may vary with disease activity. Patients with an elevated ESR and CRP are more likely to have polyarticular disease and a worse prognosis.

Hyperuricaemia is seen in 20% patients and is not due to the extent of skin involvement but related to the increased metabolic activity seen in patients of psoriasis[2]. Sometimes this hyperuricaemia is mistaken as gouty arthritis, but the presence of nail changes (pitting and onycholysis)/ dactylitis/DIP involvement differentiates these two clinical entities.

There are five clinical and overlapping subsets of psoriatic arthritis. DIP joint involvement is the most characteristic pattern. Dactylitis, enthesitis, and tenosynovitis are common musculoskeletal features accompanying psoriatic arthritis. There is a genetic predisposition to psoriatic arthritis as evident by many studies, including twin studies, family studies, and genome wide association studies (GWAS)[3]. Epidemiological studies have found that first degree relatives of psoriatic arthritis patients are 27 to 50 times more likely to develop arthritis. Upto 40% patients with psoriatic arthritis have a family history of psoriasis. Psoriatic arthritis is a polygenic disorder[3]. GWAS have identified a number of possible genes, among them HLA-B38 and HLAB39 are associated with psoriatic arthritis and HLA B27 is associated with sacroiliitis and spondylitis.Notably only 50% of patients with psoriatic sacroiliitis/spondylitis are HLA B27 positive.

Current classification criteria for psoriatic arthritis is – CASPAR (classification of psoriatic arthritis)[4]



Classification of Psoriatic-Arthritis:
CASPAR Criteria

To meet the CASPAR criteria for PsA, a patient must have inflammatory articular disease (joint, spine, or entheseal) and score ≥3 points based on these categories.

	POINTS
1. Evidence of psoriasis Current psoriasis Personal history of psoriasis Family history of psoriasis	2 or 1 or 1
2. Psoriatic nail dystrophy Pitting, onycholysis, hyperkeratosis	1
3. Negative test result for rheumatoid factor	1
4. Dactylitis Current swelling of an entire digit History of dactylitis	1 or 1
5. Radiologic evidence of juxta-articular new bone formation Ill-defined ossification near joint margins on plain x-rays of hand/foot	1

CASPAR, **CA**S**S**ification criteria for **P**soriatic **AR**thritis
Taylor W et al. Arthritis Rheum 2006;54:2665-2673

ASAS

Seronegative arthritides like ankylosing spondylitis or psoriatic arthritis may involve the sternoclavicular joint. The joint is involved in 90% of patients with severe psoriatic arthropathy, and this is clinically significant in 50% cases[5]. Whereas corresponding signs are present in only 4% of patients with ankylosing spondylitis[6]. As in our case, patient presented with unilateral sternoclavicular joint swelling without any associated psoriatic skin changes, hence, here lies the importance of good clinical examination and a careful watch for other joint involvement which clinches the diagnosis. In our case the dactylitis, onycholysis and bilateral sacroiliitis provided the clue. Generally, skin psoriasis precedes arthritis by an average of 8 to 10 years in 67% of patients but arthritis can also precede skin psoriasis or occur simulataneously in 33% of patients. Approximately 95% of patients with psoriatic arthritis have peripheral joint disease (synovitis, tenosynovitis, dactylitis, enthesitis). Other 5% have axial spine involvement, exclusively.

We hereby report this rare case of psoriatic arthritis which presented with isolated sternoclavicular joint involvement without typical dermatological changes and with subclinical sacroiliitis. This paper reinforces two important facts-firstly, the importance of sternoclavicular joint involvement in rheumatological disorders and secondly, hyperuricaemia is commonly encountered in many spondyloarthropathies and rheumatoid arthritis and so should not always be treated by xanthine oxidase inhibitors.

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"Derive happiness in oneself from a good day's work, from illuminating the fog that surrounds us."

– Henri Matisse.

CASE REPORT

JIACM 2017; 18(2): 133-35

Nitrofurantoin Induced Reversible Achromatopsia and Visual Field Constriction Defect

Geeta A Khwaja, Ashish Duggal**, Amit Kulkarni**, Neera Choudhary****, Meena Gupta*, Debashish Chowdhury******, Vikram Bohra***

Abstract

Nitrofurantoin is commonly used for the treatment and prophylaxis of urinary tract infections. Although generally a safe drug, it is sometimes associated with serious pulmonary as well as neurological side-effects. We report a patient who developed reversible achromatopsia and visual field defects after nitrofurantoin use.

Introduction

Nitrofurantoin is an antibiotic frequently used for the treatment and prophylaxis of acute and recurrent urinary tract infections (UTIs). It can cause a wide range of minor as well as serious adverse effects. Although literature is scant, defects in vision; in particular colour vision have also been described in patients taking nitrofurantoin. We report a case of acute onset achromatopsia with visual field constriction defect in a patient who was prescribed nitrofurantoin for urinary tract infection.

Case report

A 22-year-old female, presented to us with a 1 week history of sudden onset visual blurring in both the eyes. It was associated with a mild headache and eye pain especially on eye movement. Visual blurring was of acute onset and was noticed by her on getting up in the morning. She also noticed an inability to perceive colours and could discern them only as lighter or darker shades of gray. There was no history of associated diplopia, cranial nerve palsies, motor weakness, sensory loss, limb inco-ordination or imbalance. About 10 days prior to the onset of the visual complaints she had been diagnosed as having urinary tract infection and was receiving nitrofurantoin in a dose of 100 mg, three times a day.

On examination, vitals were stable and general physical, respiratory, cardiac and abdominal examination was unremarkable. Besides visual defects, higher mental functions and rest of the neurological examination was also normal. On bedside testing she complained that while the central portion of the visual field was clear, the peripheral field was blurred, especially for near objects. She could read written text but had difficulty in perceiving colours. Pupils were normal in size and reaction (both direct and consensual) and there was no relative afferent pupillary defect. The extraocular movements (both saccades and pursuit) were normal without any nystagmus. On formal testing, visual acuity was 6/18 in both the eyes and fundus was normal with a cup: disc ratio of 0.3: 1. On colour vision testing using Ishihara charts, there was red-green anomaly and the patient was unable to read the digits.

Investigations revealed a normal haemogram, kidney and liver function tests. Connective tissue profile was also normal. Perimetery showed constriction of bilateral visual fields (Fig. 1). VEP was normal and revealed a P100 latency of 101 ms in the left eye and 100 ms in the right eye (Fig. 2). MRI brain with orbital cuts was normal.

A diagnosis of nitrofurantoin induced achromatopsia with visual field constriction defect was entertained and the drug was stopped. Her colour vision and field defect improved gradually over the next few days and recovered fully within 2 weeks of discontinuing nitrofurantoin.

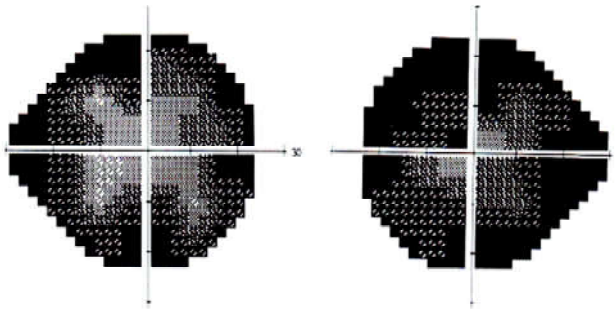

Fig. 1: *Perimetery showing peripheral constriction of visual fields in both eyes.*

Discussion

Nitrofurantoin is a synthetic nitrofuran derivative that is used for the prevention and treatment of infections of the urinary tract since 1953[1]. The antimicrobial activity of nitrofurantoin requires the action of intracellular nitrofuran reductase

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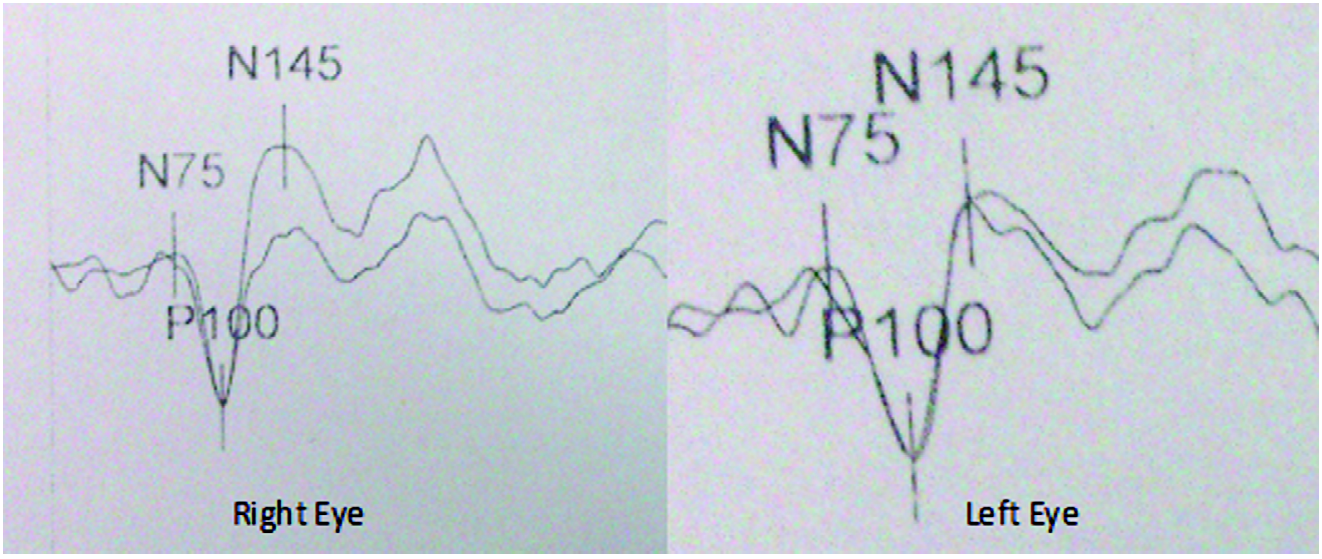

Fig. 2: *Normal VEP with a P100 of 101 ms in the left eye and 100 ms in the right eye.*

enzyme and it has a broad spectrum of activity against most gram-negative and many gram-positive organisms[2]. Bacteria that are susceptible to nitrofurantoin rarely become resistant during therapy because of the need for multiple genetic mutations to confer resistance. As resistance to fluoroquinolones and other drugs used for the treatment of UTI is increasing, nitrofurantoin, which was once used only rarely, is becoming an increasingly desirable option. Nitrofurantoin is generally well tolerated and most commonly causes a harmless brown discoloration of urine. The most common untoward effects are nausea (8%), headache (6%) and rash (6%)[3]. The incidence of adverse effects may increase with declining renal function as a result of decreased elimination and therefore increased serum concentration. More serious adverse events, including pulmonary (acute interstitial pneumonia and chronic pulmonary fibrosis), hepatic (cholestatic jaundice and chronic active hepatitis) and haemolytic reactions (leukopenia, granulocytopenia, haemolytic anaemia) are fortunately rare with a total incidence of less than 0.003%[4]. Neurological adverse effects are also rare and include headache, vertigo, drowsiness, muscular aches, and nystagmus. Severe polyneuropathies with demyelination and degeneration of both sensory and motor nerves have also been reported particularly in patients with impaired renal function and in persons on chronic suppressive therapy. Ophthalmological adverse effects include amblyopia, nystagmus, optic neuritis and dyschromatopsia but their exact incidence is not known[5].

Achromatopsia refers to a complete lack of colour perception, with the subject seeing objects or images only as black, white or shades of grey. Dyschromatopsia refers to partial loss or distortion of colour vision[6]. It is most commonly due to an inherited condition or may be acquired by diseases of the optic nerve or retina. Acquired dyschromatopsias can be caused by degenerative diseases, toxic exposures, metabolic disorders, inflammatory diseases, and cerebral insults (Table I)[6]. A large number of drugs can cause dyschromatopsia even when administered in therapeutic doses. Effects of most of the drugs are minor, reversible, and are frequently overlooked. Problems usually arise when patients with pre-existing colour vision abnormalities (anomalous trichromacy or dichromacy) have their colour perception further degraded by drug effects[6]. It is possible that our patient too had a pre-existing sub-clinical defect in colour perception which was degraded acutely by nitrofurantoin leading to achromatopsia.

Acquired colour vision defects or dyschromatopsias are classified into three broad categories. Type I defect is associated with retinal diseases, especially those involving photoreceptors of the posterior pole. It is a red/green defect with predominant damage to the function of the long-wavelength (red) sensitive cones. Type II defects are also red/green defects but are associated with damage to the function of medium-wavelength (green) cones. Type II dyschromatopsias are caused by diseases of the optic nerve such as optic neuritis, retrobulbar neuritis and optic atrophy. Type III dyschromatopsias are characterised by blue/yellow hue discrimination defects and are usually seen in nuclear cataract, glaucoma and chorioretinal degeneration. The various drugs that affect colour perception are usually associated with one of these three types of defects. Drugs like ethambutol, damage the pathways fed by foveal cones leading to a red-green defect with a relative preservation of blue/yellow hue discrimination because the fovea lacks blue sensitive cones. On the other hand, toxic retinopathy

Table I: Causes of dyschromatopsia.

Hereditary disorders of colour perception: Congenital X-linked dyschromatopsias
Acquired dyschromatopsias
Local vascular occlusive diseases: Retinal artery occlusion/choroidal arterial occlusion
Degenerative diseases: Autosomal dominant optic atrophy/senile macular degeneration/chorioretinal degeneration/Leber's hereditary optic neuropathy (LHON)/ Behr's optic nerve atrophy
Metabolic disorders: Vitamin B12 deficiency/diabetes
Inflammatory diseases: Optic neuritis/retrobulbar neuritis/chorioretinal inflammation
Cerebral disorders: Stroke/tumours
Toxins: Tobacco/Methyl alcohol/ethyl alcohol/lead/ thallium/sulfur-carbon compounds drugs • Antidiabetics (oral) • Antipyretics and analgesics: Acetaminophen and salicylates • Antibiotics: Chloramphenicol/chlortetracycline/ nitrofurantoin and its derivatives/nalidixic acid/ erythromyocin/ethambutol/ethionamide/isoniazid/ streptomycin/sulfonamides • Antifungal: Griseofulvin • Antimalarials: Chloroquine/quinine/quinidine • Antineoplastic: Mercaptopurine/vincristine • Cardiac and vascular: Digoxin/amiodarone • Diuretics:Thiazides/chlorothiazide

as for example caused by chloroquine, commonly presents as a loss of perifoveal visual field (ring-shaped scotoma), which in turn produces greater impairment of blue/yellow than of red/green hue discrimination. Nitrofurantoin has been reported to cause both type I and II dyschromatopsia[6].

Our patient had a peripheral constricting field defect in addition to a red-green defect on Ishihara test, suggestive of a type I or II dyschromatopsia, which resolved within two weeks of stopping nitrofurantoin. VEP may be normal unless the toxin damages the myelin sheaths of ganglion cell axons, particularly in the papillomacular bundle. In our case also, the VEP was normal and she could read written text despite the constriction of visual fields and a loss of colour vision.

To conclude, this case highlights a rare but important adverse effect of nitrofurantoin. It is important to be aware of this neurotoxic effect so as to prevent further damage and avoid unnecessary investigations and treatment in patients presenting with dyschromatopsia and field defects. As seen in our case, a timely discontinuation of the drug can lead to a reversal of the colour and field defects.

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"Water and air, the two essential fluids
on which all life depends,
have become global garbage cans."

– Jacques-Yves Cousteau.

CASE REPORT

JIACM 2017; 18(2): 136-39

Primary Disseminated Histoplasmosis: A Case Report and Review of Literature

Atul Bhasin, RK Singal**, Vivek Pal Singh***, Anil Vardani**

Abstract

Disseminated histoplasmosis (DH) caused by dimorphic fungus Histoplasma capsulatum is an aerosol acquired infection particularly reported in patients with immunocompromised status, especially in HIV infection. The other risk factors for DH are immunosuppressive drugs, impaired cellular imunity, haematological malignancies, organ transplant, dialysis and extremes of ages. Sub-clinical infection with H. Capsulatum is common in persons residing in disease-endemic areas, whereas manifestation of disease becomes apparent with the onset of severe immunocompromised state (CD 4 count < 200/μl). DH in non-HIV setting is uncommon and infrequently reported.

We report a case of disseminated histoplasmosis in young immunocompetent Indian male who presented to us with history of frequent hospitalisations elsewhere and multi-organ involvement.

Key words: Histoplasmosis; immunocompetent; amphotericin B.

Introduction

Infection *with Histoplasma capsulatum* is endemic in many parts of the world, particularly American subcontinent and Columbia. Histoplasma is an oppurtunistic fungus of low virulence and infection occurs when there is a transient or persistant decrease in host immune response or some anatomical alteration, (e.g., emphysema) leading to a focus of histoplasma proliferation. After initial exposure to the fungus, the infection is self-limited and restricted to the lungs in 99% of healthy individuals. The remaining 1%, however, progress to either disseminated or chronic disease involving the lungs, liver, spleen, lymph nodes, bone marrow or rarely, the skin and mucous membranes[1]. Though, rare, it has been reported to affect immunocompetent individuals. The disease may present as a transient self-limiting flu-like illness with pulmonary symptoms or as a chronic multiorgan disease, which can be confused for tuberculosis or a malignancy[2].

Case report

A 26-year-old male, resident of Madhya Pradesh, India presented to us on 23/6/2016 with moderate fever with chills, cough with scanty expectoration and generalised weakness. Patient was asymptomatic approximately three months back, when initially he was admitted in a private hospital in Gwalior and was treated as falciparum malaria. He was discharged from the hospital after one week in a stable condition. Thereafter he developed jaundice and was treated as acute hepatitis elsewhere and was discharged again after ten days in a stable condition. He was readmitted in a private hospital in Gwalior on 7/5/2016 with altered sensorium and was found to be having anaemia, thrombocytopenia and was treated for cerebral malaria and discharged in a satisfactory condition.

Again on 22/06/2016, he developed fever, swelling over feet and face, breathlessness and generalised weakness and went to same hospital at Gwalior, where he was found to be having moderate thrombocytopenia (platelet count 60,000/mm^3). He took LAMA on 23/6/2016 and reported to us. He was conscious, GCS was 15/15, temp was 103° F, HR: 120/min, BP: 110/70 mmHg. General examination revealed severe pallor and bilateral pitting pedal oedema. Patient was hypoxic. SpO2 was 88 % on ambient air. Systemic examination revealed bilateral reduced basal air entry with vesicular breath sounds and hepatosplenomegaly.

Routine investigations are enumerated in Table I. Cultures were unremarkable. Chest X-ray showed diffuse bilateral alveolar infiltrates (Fig. 1). CECT chest revealed bilateral extensive ground glass opacities with areas of consolidation and air bronchogram and pleural effusion (Fig. 2). CECT abdomen confirmed ultrasound findings of hepatosplenomegaly along with dilated splenic vein and an ill defined focal hypodense area in parenchyma, confined within splenic capsule, suggestive of splenic infarction. HIV 1 and 2 was non-reactive (repeated second time over a period of three months). However, CD4 count was low (138 cells/mm^3). Serology for brucella and leptospira was negative.

Bone marrow aspirate (BMA) stains with Periodic acid schiff (PAS) stain and bone marrow biopsy stains with Gomori's

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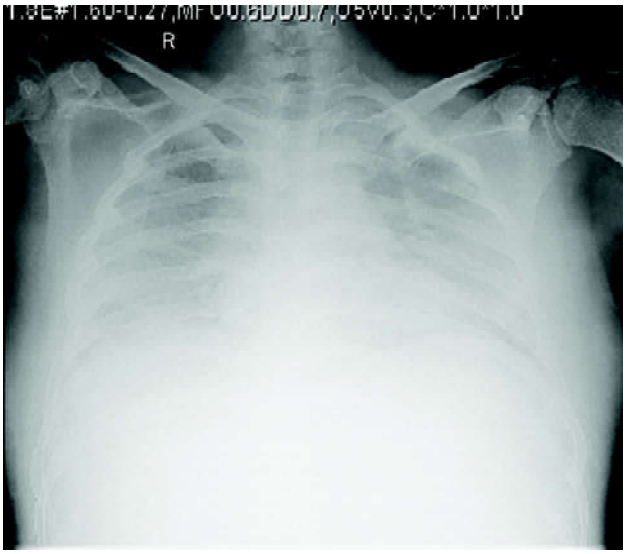

Fig. 1: *Chest X-ray showing diffuse bilateral alveolar infiltrates.*

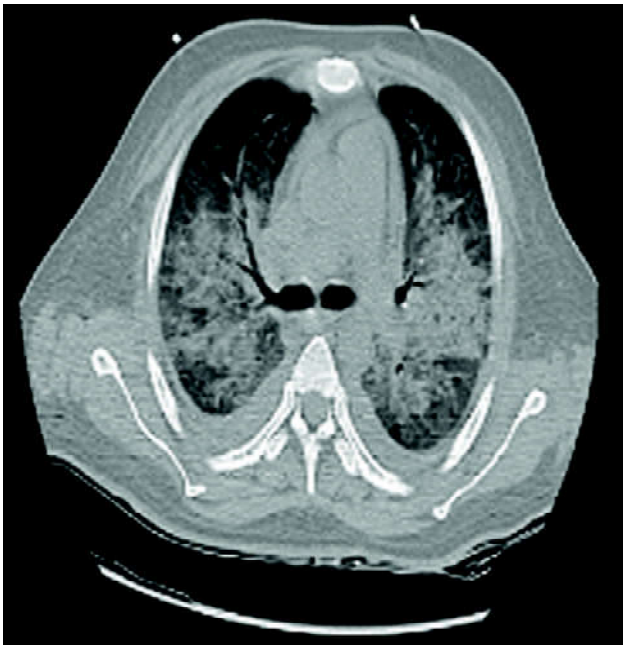

Fig. 2: *CECT chest showing bilateral extensive ground glass opacities with areas of consolidation and air bronchogram and pleural effusion.*

Methenamine Silver revealed yeast like bodies with positive staining of the cell wall suggestive of extensive involvement (both intra- and extra-cellular) yeast like organisms, morphologically most consistent with *Histoplasma capsulatum* (Fig. 4, 5). Blood sample was sent for fungal serology at AIIMS, New Delhi and same was negative for histoplasma and cryptococci, while BMA morphology was consistent with histoplama. Blood culture was sent to Department of medical mycology at Vallabhbhai Patel Chest Institute, New Delhi and it was

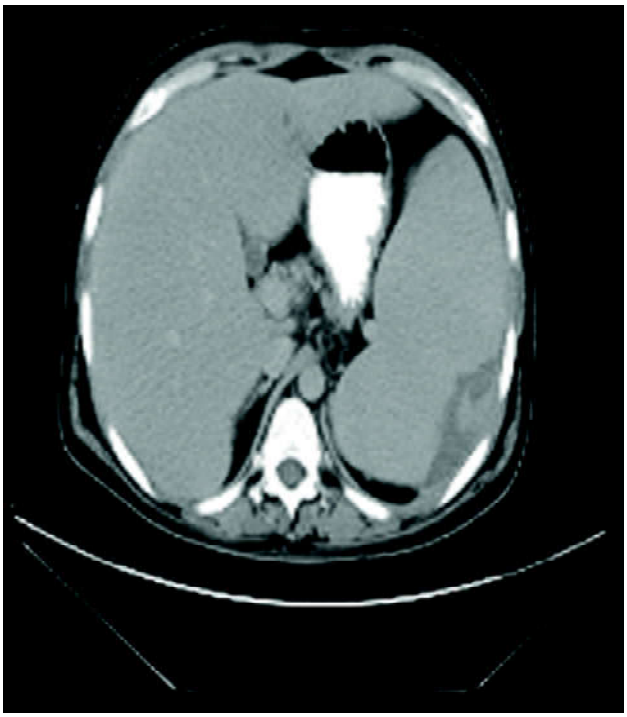

Fig. 3: *CECT abdomen showing hepatosplenomegaly along with dilated splenic vein and splenic infarct.*

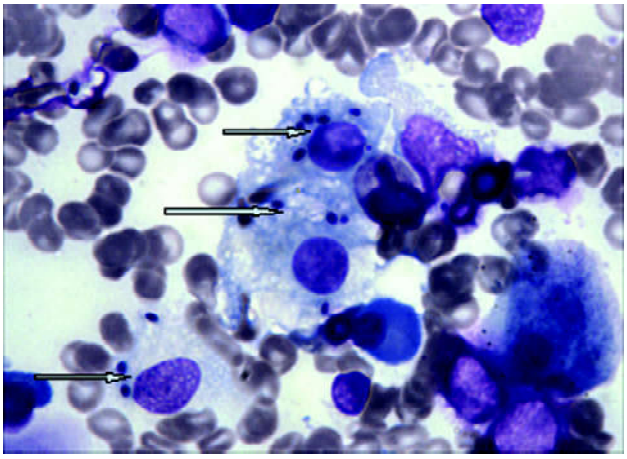

Fig. 4: *Bone marrow aspirate with PAS staining showing histiocytic cells with engulfed fungal spores (arrow).*

reported to have yielded heavy growth of *Histoplasma capsulatum*.

Patient was initially managed with BIPAP support and broad spectrum antibiotics. Inj Amphotericin B (0.5 mg/kg/day) was given followed by itraconazole. He was also given multiple component blood transfusions.

Patient responded satisfactorily to the treatment. His CD 4 counts on discharge were 412/mm^3. He was discharged from hospital in satisfactory condition. Patient is under follow-up and has improved over period of time.

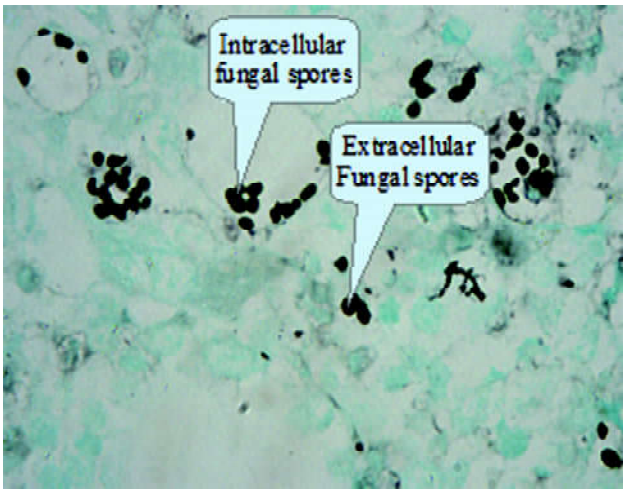

Fig. 5: *Bone marrow biopsy with Gomori's Methenamine Silver (GMA) showing both intra- and extra-cellular fungal spores (arrow).*

Table I: Routine haematology and biochemistry.

Haemoglobin	8.9 gm%
Total leucocyte count	5,400/mm^3
Platelet count	20,000/mm^3
Peripheral blood smear	Shift to the left with few band forms and toxic granules
Blood urea	27 mg/dl
Serum creatinine	0.5 mg/dl
Serum albumin	3.4 gm/dl
Bilirubin	0.6 mg/dl
ALT	21 U/L
AST	16 U/L
Alkaline phophatase	82 U/L
INR	2.1 sec

Discussion

Histoplasma capsulatum is a dimorphic fungus found in soil contaminated with bird and bat droppings. Primary route of infection is aerosol inhalation leading to primary lung infection. Classic histoplasmosis is also called Darling's disease. It is a deep mycotic infection caused by one of two species *Histoplasma capsulatum* is found in the Americas and the tropics, particularly the Ohio and Mississippi river valleys of North America. *Histoplasma dubosii* is prevalent in Africa. In India, endemic cases of histoplasmosis have been reported in West Bengal and sporadic cases have been reported in southern India. Further reports of histoplasmosis from nonendemic regions are very rare[1,2].

The severity of primary infection depends upon the inhaled fungal load and host's immune response, particularly CD4 T-cells. Disseminated histoplasmosis (DH) may occur either after recent exposure or upon endogenous reactivation of latent foci. The risk factors for DH are extremes of ages, haematologic and other malignancies, immunosuppressive therapy and advanced HIV infection[1].

Patients suffering from acute pulmonary infection may either be asymptomatic or present with symptoms similar to the flu, such as fever, shivering, dry cough, pleural or substernal chest pain, malaise, myalgia and arthralgia, as well as erythema (multiforme or nodosum). Late complications may result from intense immune response of the host, characterised by fibrosis and enlargement of hilar or mediastinal lymph nodes, leading to compression of adjacent structures as well as to secondary complications. Chest X-rays may be normal or may reveal diffuse infiltrates, hilar and mediastinal lymph node enlargement, or diffuse granular opacities. Chronic pulmonary infection may resemble pulmonary tuberculosis[1-3].

Primary lung infection is frequently followed by involvement of liver and spleen. DH is a less common manifestation of the disease and mainly affects immunocompromised patients. The severity of symptoms reflect the degree of patients immunocompetence. The most common signs and symptoms are fever, generalised weakness, weight loss, hepatomegaly, splenomegaly, lymphadenopathy, oropharyngeal ulcerations, cytopenias (anaemia, leucopenia, thrombocytopenia), endocarditis, GI bleed and chronic lymphocytic meningitis[3,4].

A diagnosis of pulmonary disease caused by fungi is confirmed through analysis of sputum cultures, tracheal aspirate, bronchoalveolar lavage fluid or biopsy samples. Diagnosis can also be made through culture or histopathological analysis of other affected organs, fluids and tissues, serology, complement fixation or immunodiffusion[1,5].

A 6- to 12-month course of antifungal drugs (amphotericin B, itraconazole or ketoconazole) is recommended. Mortality of non-treated, severe cases is 80%, which can be reduced to less than 25% with antifungal therapy. Many patients diagnosed with acute histoplasmosis do not require specific treatment and will recover spontaneously. However, treatment is recommended for all cases of progressive disseminated histoplasmosis. Among severe cases, the mortality rate is 50%, even when amphotericin B therapy is administered. However, 98% of mild cases respond to the same treatment[1,5].

This case highlights the fact that disseminated histoplasmosis, though rare, can present sporadically and a high index of suspicion with a robust histopathalogical and microbiological support is required for accurate diagnosis

and treatment of a potentially lethal disease.

Acknowledgement: Dr Pawan Kirtani, Consultant Pathology, BLK Super Speciality hospital, Pusa Road, New Delhi - 110 005.

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"The bodhisattva should adopt the same attitude towards all beings,
his mind should be even towards all beings,
he should not handle others with an uneven mind,
but with a mind which is friendly, well-disposed, helpful,
free from aversions avoiding harm and hurts."

– PERFECTION OF WISDOM.

CASE REPORT

JIACM 2017; 18(2): 140-43

Recurrence of Achalasia Cardia Presenting as Chronic Cough

V Sengal, G Nair**, R Shah*, A Uppe***, A Das*****, P Agarwal*****

Abstract

A case of achalasia cardia presenting with cough and treated as cough-variant asthma has been discussed. This association is not very common. The mechanism of chronic cough in diseases of oesophageal origin can be due to oesophageal retention of food and secretions, and then aspiration into the lungs. The special feature of this case is that the patient's daughter is a known case of bronchial asthma with multiple admissions in the respiratory medicine ward.

Key words: Respiratory symptoms, oesophageal diseases, pulmonary infections.

Introduction

Chronic cough with diurnal variation may be of respiratory as well as non-respiratory origin. Bronchial asthma, COPD, bronchiectasis, allergies or any infection of respiratory tract are the respiratory causes. Certain disorders of the gastrointestinal tract such as GERD, achalasia cardia may cause aspiration pneumonia, microabscesses and rarely bronchiectasis, lung abscess, and atelectasis leading to chronic cough. Achalasia cardia results from the degeneration of neurons in the oesophageal wall. It is caused by loss of ganglion cells within the oesophageal Auerbach's plexus causing dilatation of the lower oesophagus.

Case report

A 57-year-old, housewife came with complaints of dry cough since 2 years and difficulty in breathing since a year. Her cough had no seasonal exacerbation and worsened at night and on lying down. She was awakened every night because of its severity. Breathlessness was gradual in onset, not progressive, with no seasonal exacerbation, more after meals particularly and after lying down or walking a short distance, classified MMRC grade 2. It was relieved with rest and partially with DPI. She had no fever, chest pain, weight loss or haemoptysis. She was a known hypertensive since 10 years for which she was on tablet Telmisartan 40 mg once a day in the morning, and a known case of hypothyroidism since 5 years, taking tablet thyroxine 25 mcg once daily in morning. She did not give any history of diabetes, ischemic heart disease or tuberculosis in the past. She gave history of undergoing an abdominal surgery 20 years ago, but she could not recollect any more details regarding its cause and nature. Her daughter was a diagnosed asthmatic requiring bronchodilators regularly and was admitted two to three times in last two years under our care for the same. She denied any addiction to tobacco chewing, smoking or exposure to wood chullah smoke. She was diagnosed as cough variant asthma by her family physician two years ago and was being treated accordingly with inhaled bronchodilators, oral and inhaled steroids since then. However, her symptoms did not improve significantly.

On examination, the patient was mildly obese with a BMI of 35 Kg/m^2, vitals stable with blood pressure of 130/78 mmHg, pulse rate of 84 per minute, respiratory rate of 18 per min and room air SPO2 of 98%. General examination revealed no abnormality. Her upper respiratory tract was normal with no hypertrophied turbinates or deviated nasal septum. On lower respiratory tract examination, bilateral breath sounds were equal and no adventitious sounds were present. On abdominal examination mid-line epigastric scar of surgery

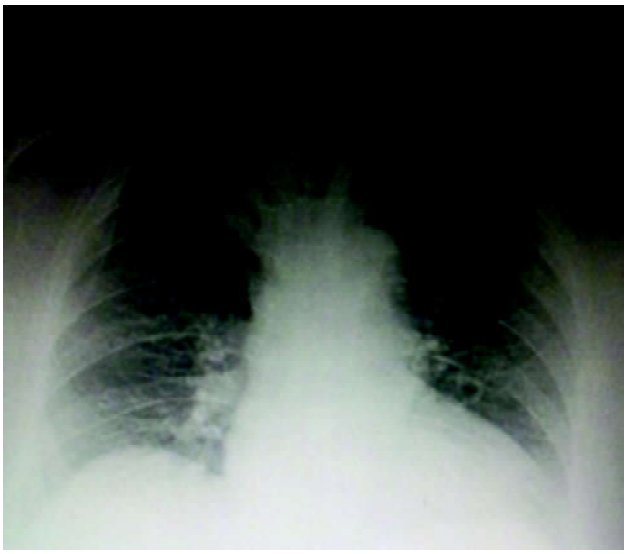

Fig. 1: *X-ray chest (PA view) showing right paratracheal opacity.*

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was visible, however, there was no tenderness or any swelling in the abdomen. Other systems were unremarkable. The routi ne investigations done on admission were reported as Hb% - 14.1 gm/dl; total WBC count - 6,700/cmm; N - 54, L - 40, M - 5, E - 1; ESR - 16 mm. HIV negative; RBS - 117 mg/dl; serum creatinine - 0.9 mg/100 ml; blood urea - 77 mg/100 ml; urine routine showed no abnormality. Chest X-ray revealed a right paratracheal opacity. PFT was suggestive of mild obstruction and 2D echo reported LV ejection fraction of 60% with diastolic dysfunction.

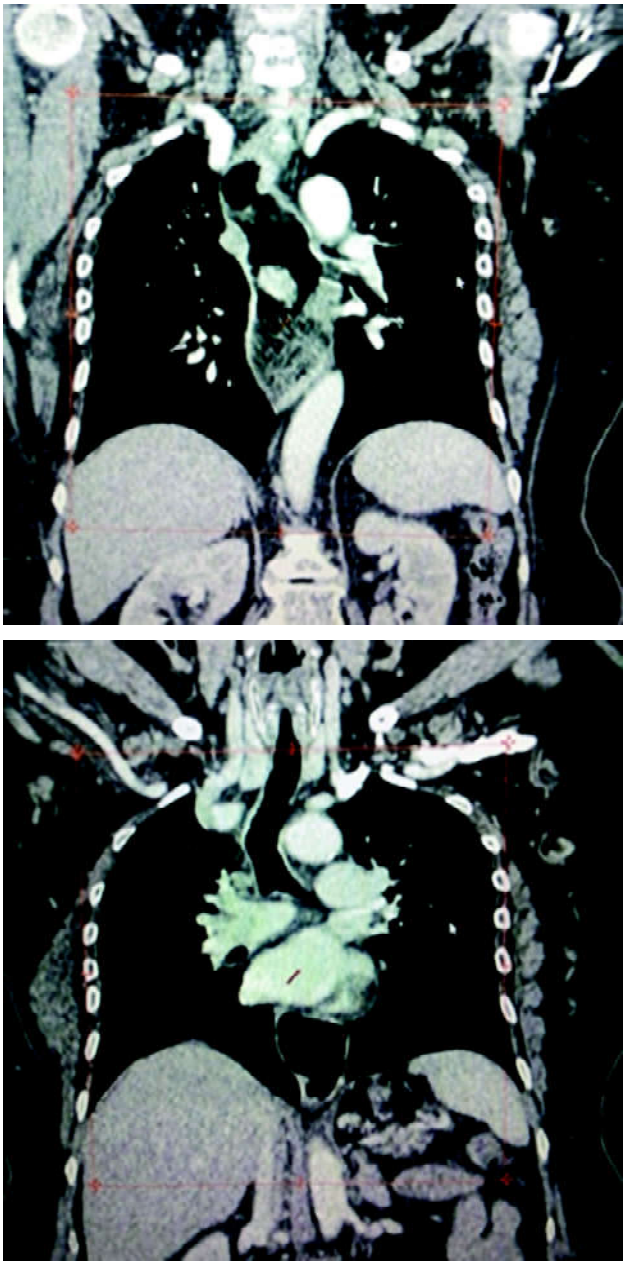

Fig. 2 and 3: *Mediastinal window coronal section, showing dilated distal part of oesophagus with food.*

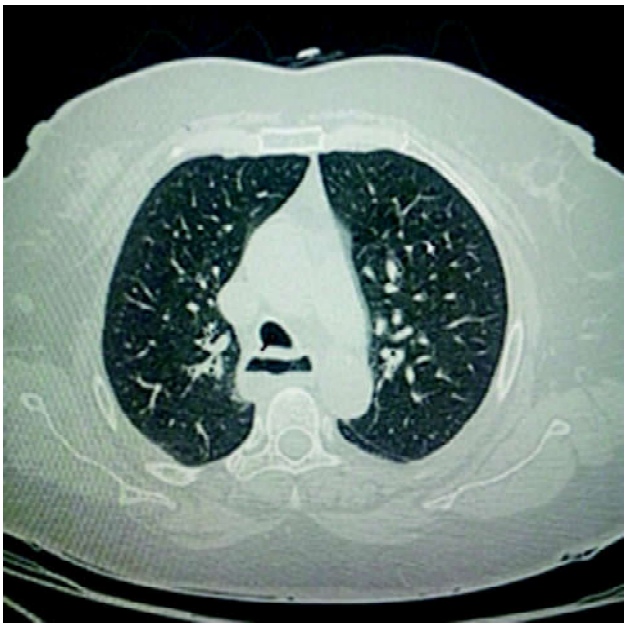

Fig. 4: *Lung window transverse section, showing dilated oesophagus with normal lung parenchyma.*

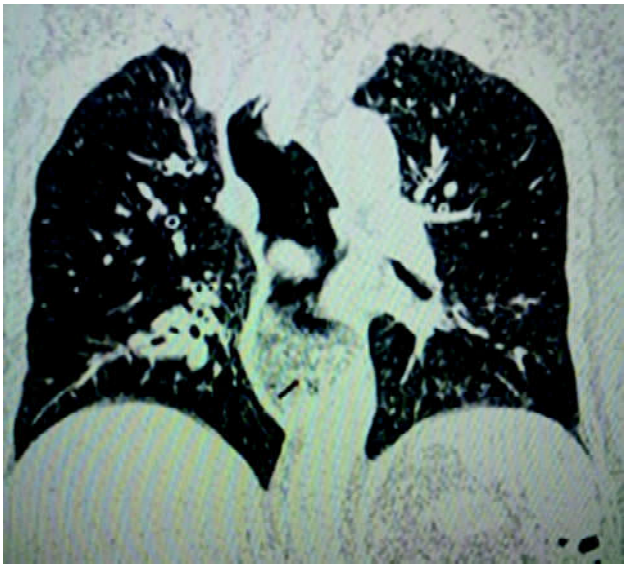

Fig. 5: *Lung window coronal section, showing dilated oesophagus with normal lung parenchyma.*

Given her daughter's history of asthma, we too had given her a probable diagnosis of cough variant asthma; obstructive sleep apnoea needed to be ruled-out given her obese status and co-morbidities of hypertension and hypothyroidism. Yet, based on findings of the chest X-ray we advised her for a high resolution CT of the chest. HRCT with CECT chest revealed mild-to-moderate dilatation of the mid and distal third of the oesophagus with abrupt narrowing of the gastro-oesophageal junction. No abnormal enhancing soft tissue was noted at the gastro-oesophageal

junction. The lung parenchyma was normal in appearance.

On repeated enquiry she told us that the cough every night was preceded by regurgitation of undigested foods and liquids which even came out through the nose while sleeping and she was a wakened by it. She presumed that she was an asthmatic and that these details had no relevance to her current symptoms. Her old medical records suggested that she was diagnosed as a case of achalasia cardia for which pneumatic balloon dilatation was done in 1998 and Heller's myotomy done in 2004, due to recurrence.

She was hence diagnosed as having a recurrence of achalasia cardia giving rise to persistent continuous cough. She was referred to surgery department for further treatment where she was advised manometry and myotomy. She was counselled regarding the respiratory complications of this condition and need for immediate intervention given the severity of her symptoms. Patient underwent myotomy and since then has been relieved of her symptoms.

Discussion

Achalasia is a very rare disorder with an annual incidence of approximately 1.63 cases per 100,000 individuals and prevalence of 10.82 cases per 100,000 individuals[1]. Men and women are affected with equal frequency. It is usually diagnosed in patients between the ages of 25 and 60 years. In achalasia, there is loss of inhibitory innervation in the LES which causes the basal sphincter pressure to rise, and this renders the sphincter muscle incapable of normal relaxation. In the smooth muscle portion of the oesophageal body, the loss of inhibitory neurons results in aperistalsis. In addition to the LES dysfunction that is a sine qua non for achalasia, there may also be asubtle defect in reflex relaxation of the upper oesophageal sphincter (UES)[2].

The cause of the inflammatory degeneration of neurons in achalasia is unknown. The observation that achalasia is associated with HLA-DQw1 and that affected patients often have circulating antibodies to enteric neurons suggest that achalasia may be an autoimmune disorders. Some investigators have proposed that achalasia results from chronic infections with herpes zoster or measles viruses but data have been inconclusive. Inheritable forms and genetic causes are also postulated, e.g., Triple A syndrome (Achalasia, Alacrima, Addisons disease) also known as Allgrove Syndrome[3].

Certain recognised diseases can also cause oesophageal motor abnormalities similar or identical to those of primary achalasia. This condition is cal ed secondary or pseudo achalasia, causes being Chagas disease (caused by Trypanosoma Cruzi), malignancy (being the most common cause of secondary achalasia) and others such as amyloidosis, sarcoidosis, neurofibromatosis, eosinophilic gastroenteritis, multiple-endocrine neoplasia type 2 B, juvenile Sjögren's syndrome, systemic sclerosis[2]. Its common presenting symptoms are dysphagia for solids and liquids, regurgitation of food, chest pain, retrosternal fullness or burning especially post-meals. Some of these symptoms overlap with those of GERD. Hence often undiagnosed and mistreated. Some cases of achalasia may present with atypical symptoms such as cough, breathlessness, bronchorrhoea, wheezing, repeated episodes of respiratory infections, hence emphosising the importance of respiratory symptoms arising from diseases originating from other systems. Thus if not investigated thoroughly, this condition may be missed, as it occurred with our patient.

Cough is a very common symptom of many diseases. Each cough occurs through the stimulation of a complex reflex arc. This is initiated by the irritation of cough receptors which are found in the trachea, main carina, branching points of large airways, and more distal smaller airways; also, they are present in the pharynx. Laryngeal and tracheobronchial receptors respond to both mechanical and chemical stimuli. In addition, more airway receptors are in the external auditory canals, ear drums, paranasal sinuses, pharynx, diaphragm, pleura, pericardium, and stomach. These are probably mechanical receptors only, which can be stimulated by triggers such as touch or displacement[4]. Its occurrence can therefore be attributed to many causes: pulmonary and non-pulmonary.

The importance of our case is to highlight not only non-pulmonary causes of respiratory symptoms, but also pulmonary complications of achalasia cardia, for many may present directly to us with these complications. Nocturnal aspiration is reported to cause recurrent aspiration pneumonitis in 10 per cent of all untreated patients of achalasia. Other complications are aspiration pneumonia, lung abscess, chronic pulmonary infections with atypical mycobacteria. *Mycobacterium fortuitum*, a non-tuberculous rapidly growing acid fast bacterium, resistant to most antibiotics, may produce pulmonary infection by developing in a fatty fluid supernatant retained in the oesophagus. Oil, which is cleared more slowly than other substances, by the tracheobronchial tree, impairs phagocytosis, thus favouring the development of these atypical mycobacterial infections. Among the acute situations which may occur secondary to achalasia, airway obstruction has been reported to require immediate intubation and myotomy[5]. Massive pulmonary aspiration remains one of the most catastrophic events that may occur during initiation of surgical treatment for achalasia patients. Recurrent aspiration can lead to chronic interstitial changes/fibrosis, clinically represented as intermittent

cough and waxing and waning pulmonary lesions. The term diffuse alveolar bronchiolitis (DAB) has been proposed to define a clinical entity that is characterised by achronic inflammation of bronchioles caused by recurrent aspiration[6].

Diagnosis is with manometry, barium esophagram, imaging, and upper endoscopy. There is no cure for achalasia. Treatment is focused on palliating symptoms by decreasing LES pressure to facilitate emptying of oesophageal contents. This can be accomplished by mechanical disruption of the muscle fibres of the LES, (e.g., with pneumatic dilation or surgical myotomy) or by biochemical reduction in LES pressure, (e.g., with injection of botulinum toxin). Treatment options are pneumatic balloon dilatation, hellers myotomy, botulinum toxin injection and a more recent POEM (Peroral endoscopic myotomy). None of these give a definitive cure, all having recurrence rates, differing from one other, myotomy having the least.

Conclusion

Gastrointestinal causes of chronic cough have to be kept in mind, owing to the anatomical closeness of the GI tract and respiratory system, GERD being one of them. We report this rare case of achalasia cardia presenting with persistent nocturnal cough in a patient whose daughter was already under our treatment for intermittent asthma.

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"Bones can break,
muscles can atrophy,
glands can loaf,
even the brain can go to sleep
without immediate danger to survivial.
But, should the kidneys fail,
neither bones, muscles, glands, nor brain could carry on."

– Dr. Homer W. Smith.
(From *Fish to Philosophy)*

CASE REPORT

JIACM 2017; 18(2): 144-48

Steroid Responsive Relapsing Remitting Seronegative Autoimmune Brainstem Encephalitis: A Case Report with Long-Term Follow-up

Geeta A Khwaja, Ashish Duggal****, Abhilekh Srivastava****, Vijay Ghuge****, Neera Chaudhury***, Debashish Chowdhury***

Abstract

Autoimmune mediated encephalitis (AME) represents a complex syndrome with diverse immunologic associations and variable clinical manifestations depending on the predominant site of involvement in the neuraxis and the nature of antibodies detected. Diagnosis and management of AME remains a challenge, especially in cases that are seronegative. Goal of therapy is to reverse or prevent further disease progression and to minimise the associated cognitive impairment. We report a case of non-infective, antibody-negative, steroid responsive 'Brainstem encephalitis' with a 2- and -a-half-years history of relapsing-remitting cerebellar ataxia, dysphagia and behavioural changes with MRI T2 hyper intensities in the region of the brainstem, basal ganglia and mesial temporal lobes. All clinically suspected cases of AME, even if seronegative, warrant a trial of immunotherapy as a diagnostic test. Responders should receive long-term maintenance immunotherapy to prevent further relapses, as highlighted by our case.

Key words: Autoimmune encephalitis, brainstem encephalitis, rapidly progressive dementia.

Introduction

Brainstem encephalitis is a rare syndrome characterised by a variable combination of multiple cranial nerve palsies, cerebellar ataxia, long tract signs (corticospinal, spinothalamic, posterior column) and altered level of consciousness[1]. Aetiology of brainstem encephalitis can be broadly classified as infectious, autoimmune and paraneoplastic. Patients with autoimmune mediated encephalitis (AME) can present with symptoms and signs suggestive of a neurodegenerative illness or a subacute encephalopathy but show a gratifying response to immunotherapy. Diagnosis is based on antibody detection and can become challenging in patients who are seronegative. We report a patient who presented with a relapsing-remitting brainstem encephalitis without any obvious infectious cause, a negative autoimmune profile and a good response to immunotherapy in the form of steroids.

Case report

A 40-year-old non-diabetic, non-hypertensive male, first presented to us with 8 months history of gradually progressive gait imbalance with frequent falls and a tendency to sway towards left side while walking. He also complained of some tremulousness and clumsiness of the hands with difficulty in performing activities of daily living even though he denied any history of motor weakness or loss of sensation in the limbs. Three months after the onset of these symptoms he also developed difficulty in speaking with a scanning speech and progressive dysphagia, especially for liquids. A change in his behaviour and personality was also observed by his wife around 5 months after the onset of the gait imbalance. He became disinhibited, jovial, insensitive, euphoric, overfriendly with strangers and at times made crude remarks and displayed inappropriate behaviour towards his family and friends. He also stopped taking interest in his household and other work related activities. There was a complete lack of insight with regards to his behaviour but no history of forgetfulness, hallucinations or delusions. There was no history of fever, headache, vomiting, seizures, systemic disturbance or any other significant illness in the past.

On examination, when the patient first reported to us about 2 years back, he was conscious, alert and vitals were stable. Respiratory, cardiovascular and abdominal examination was unremarkable. On higher mental status examination, new learning ability and remote memory were intact but MMSE was 23/30 with impaired orientation to time and place and serial subtraction. On cranial nerve examination, the gag reflex was bilaterally depressed but the other cranial nerves were intact. There was no motor weakness or sensory deficit but all the deep tendon reflexes were exaggerated and the plantars were bilaterally extensor. On cerebellar examination, he had a prominent gaze evoked nystagmus (left > right) with scanning, staccato speech and bilateral limb incoordination (left > right) with marked gait ataxia.

On laboratory evaluation, haemogram, blood counts, ESR and routine blood chemistry including blood sugar, LFT, KFT and serum electrolytes were normal. Blood examination was

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negative for VDRL, HIV, hepatitis B surface antigen (HbsAg), antibodies to hepatitis C virus (anti HCV). MRI brain revealed, non-enhancing hyperintensities in the midbrain and bilateral superior cerebellar peduncles, mesial temporal lobes and basal ganglia on T2 Weighted and FLAIR sequences (Fig. 1A). On cerebrospinal fluid examination there were no cells and sugar was in the normal range (76 mg/dl) but protein was elevated (130 mg/dl). EEG did not reveal any significant abnormality. Work-up for vasculitic profile was negative for RA factor, ANA, anti-ds DNA, anti SS-A, anti SS-B, c-ANCA and p-ANCA. ASO titre, CRP, serum calcium and ACE levels were in the normal range. ECG, X-ray chest, CT chest, and ultrasound abdomen done to rule-out any malignancy were also normal. Thyroid function tests and anti thyroid peroxidase antibodies were within normal range. Serum testing for NMDA receptor antibodies, anti VGKC antibodies and anti neuronal antibodies (anti-Hu, anti-Yo, anti-Ma2, anti-AMPA receptor and anti-amphiphysin) was negative.

In view of a history of a progressive cerebellar ataxia with mild dysphagia, pyramidal signs and behavioural changes along with MRI findings of bilateral symmetric signal alteration in the region of the brainstem, basal ganglia and mesial temporal lobes with a negative autoimmune profile, a diagnosis of seronegative autoimmune brainstem encephalitis was entertained.

The patient was treated with IV methylprednisone (1 g/day for 5 days) followed by oral prednisolone in a dose of 60 mg/day for a period of one month. Within 1 week of initiating therapy, there was a dramatic improvement in his gait and speech. His behavioral changes persisted but his gait and speech improved by around 70% over the next one month and he became independent for his activities of daily living. Patient was discharged on tapering doses of steroids but stopped all his medications after around 2 months. Off medication, he remained stable, without any further deterioration, for around one and a half years. He then reported back to us with a 3 weeks history of worsening dysarthria, clumsiness of the hands, gait imbalance and repeated falls. A repeat MRI brain done at this stage (Fig. 1 B and C), revealed persistent but reduced hyperintensities in the midbrain, basal ganglia and mesial temporal lobes. Other investigations including repeat imaging studies of the chest and abdomen to rule-out any malignancy were normal. In view of a fresh relapse, he was again treated with methyl-prednisone pulse therapy followed by oral steroids. Within one week of initiating steroids, there was a significant improvement in his symptoms. He returned to his previous baseline within a period of one month and has remained stable on a low dose maintenance steroid therapy (10 mg prednisolone per day) over the last 2 years.

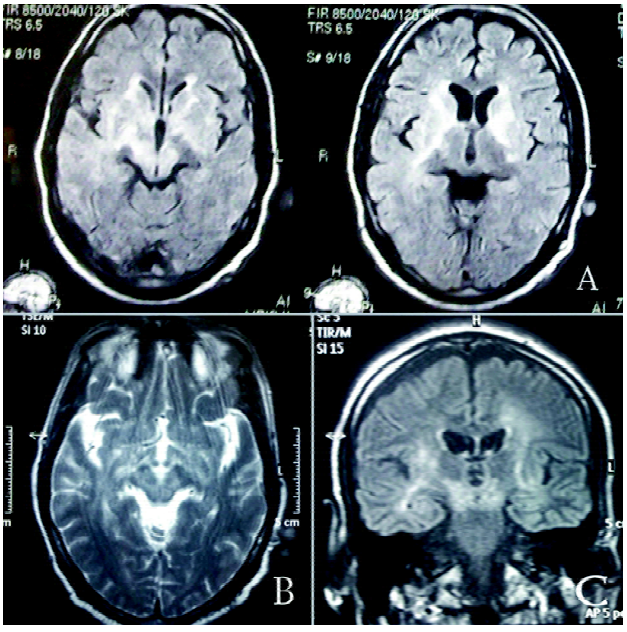

Fig. 1A: *Axial FLAIR MRI at first presentation showing hyperintensities in the midbrain, bilateral superior cerebellar peduncles, mesial temporal lobes and basal ganglia.*

Fig. 1B and C: *Axial T2 and coronal FLAIR images at second presentation showing persistent but reduced hyperintensities in the midbrain, basal ganglia and mesial temporal lobes.*

Discussion

The term brainstem encephalitis or "rhombencephalitis" refers to inflammatory disease of the brainstem that can be caused by various infectious, autoimmune and neoplastic causes (Table I)[1]. Anatomically, rhombencephalon or the hindbrain is composed of the pons, medulla oblongata and the cerebellum. Strictly speaking midbrain is not a part of the rhombencephalon, but inflammation of the midbrain is often included in reported cases of rhombencephalitis[2], as was observed in our case also. Clinically brainstem encephalitis presents with variable combinations of multiple cranial nerve palsies, cerebellar ataxia, long tract signs (corticospinal, spinothalamic, posterior column) and altered level of consciousness[1]. Our patient also presented with behavioural changes, depressed gag reflex, pyramidal signs and a prominent cerebellar ataxia suggestive of brainstem encephalitis. Cranial nerve palsies due to involvement of the cranial nerve nuclei in the brainstem have been described in approximately 75% (range 67% - 86%) cases[3]. Cerebellar ataxia due to involvement of the cerebellar pathways or the cerebellum is more common in infectious and paraneoplastic encephalitis as compared to autoimmune brainstem encephalitis. Long tract signs are less frequent in paraneoplastic cases and more common in encephalitis caused by Behcet's disease and infectious agents such as Listeria. An altered level of consciousness, occurring due to involvement of the reticular activating system, is primarily seen in infectious and less commonly in paraneoplastic encephalitis[3]. Behavioural and personality

changes are more common in paraneoplastic and infectious brainstem encephalitis due to Herpes virus and are caused by an extension of the inflammatory process to the mesial temporal lobes[4]. Our patient had florid behavioural and personality changes in the setting of a seronegative autoimmune brainstem encephalitis.

Common infectious causes of brainstem encephalitis include Listeria, enterovirus 71 and herpes viruses[1,5,6]. HSV encephalitis is most commonly associated with mesial temporal lobe involvement but infratentorial involvement may also occur. Infectious aetiology is suggested by the presence of fever, relatively rapid onset of symptoms, signs of meningism and CSF evidence of pleocytosis (usually > 100 cells/mm^3). A low CSF sugar is suggestive of bacterial infections. The absence of all these features ruled-out an infectious cause of brainstem encephalitis in our case.

In carcinomatous brainstem encephalitis, tumour cells may invade the brain parenchyma via Virchow-Robin spaces[7]. Headache, dementia, cranial nerve palsies, behaviour changes and ataxia are seen in about half the cases. CSF findings include predominantly lymphocytic pleocytosis, elevated protein and hypoglycorrhachia. The gold standard for diagnosis is CSF cytology for malignant cells, which is positive in up to 90% of cases especially after serial lumbar punctures. A normal CSF glucose and absence of malignant cells in our case, excluded the possibility of a carcinomatous brainstem encephalitis.

Immune mediated non-infectious inflammatory brainstem encephalitis may or may not be associated with vasculitis[8] (Fig. 2). Vasculitic diseases like Behcet's disease (BD), primary angiitis of CNS and SLE can be a cause of isolated or predominant brainstem encephalitis[1]. In our case, there was an absence of systemic features and workup for vasculitic disease was negative.

Non-vasculitic immune mediated causes of brainstem encephalitis include: site restricted acute disseminated encephalomyelitis (ADEM), Bickerstaff brainstem encephalitis and antibody mediated encephalitis. Site restricted form ADEM is a monophasic disorder of acute onset that can remain confined to the basal ganglia or brainstem[9]. An older age of onset, lack of an antecedent illness, and a protracted 8 months disease course, did not support the diagnosis of ADEM in our case. Bickerstaff brainstem encephalitis (BBE) and the associated Miller Fischer syndrome are part of a spectrum of diseases associated with antiGQ1b antibodies, which are considered to be pathogenic. BBE usually runs a monophasic remitting course with a slow recovery but good outcome. The syndrome is characterised by acute onset ophthalmoplegia and ataxia with or without a disturbance of consciousness and hyperreflexia. A parkinsonian picture may develop transiently during the recovery phase[10]. CSF albumino-cytological dissociation can occur although its absence does not preclude the diagnosis. In our case, the ataxia and behavioural changes were not accompanied by ophthalmoplegia and the progression of symptoms over a prolonged period of 8 months ruled-out the diagnosis of BBE.

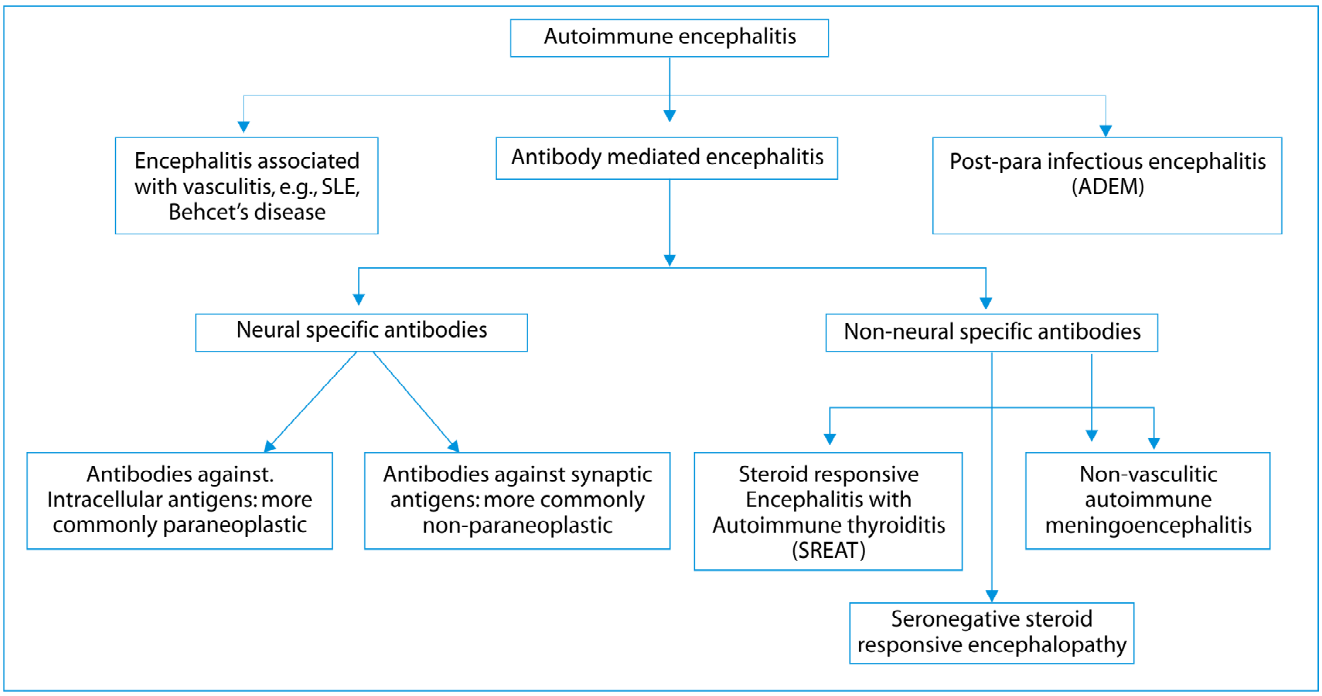

Fig 2: *Classification of autoimmune encephalitis.*

Antibody mediated encephalitis (AME) can be associated with systemic autoimmune disorders or can be paraneoplastic in nature. AME therefore represents a complex category of diseases with diverse immunologic associations characterised by interaction of auto antibodies in the CSF or serum against various neuronal or systemic antigens. AME due to neuronal intracellular or cell surface related antigens can be paraneoplastic or non-paraneoplastic in nature. AME due to intracellular neuronal antigens is more commonly associated with a malignancy and is poorly responsive to immunotherapy. AME due to cell surface related antigens is rarely associated with a neoplasm and is more responsive to immunotherapy[11]. AME can also be associated with other non-neural systemic autoantibodies such as Thyroid peroxidase (TPO) antibody (SREAT- steroid responsive encephalopathy associated with autoimmune thyroiditis), and non-organ-specific antibodies (ANA, APLA, ENA, dsDNA, ANCA and RF) in the setting of a systemic autoimmunity (NIAM - nonvasculitic autoimmune inflammatory meningoencephalitis). This group of disorders has an excellent response to steroids and is now collectively known as steroid responsive encephalopathy (SRE)[8].

The clinical manifestations of AME depend both on the type of antibodies present and the predominant site of inflammation. While some antibodies affect specific locations because of the localised distribution of the antigens, other antibodies cause more diffuse cortical and subcortical lesions. Anatomically, AME can be classified into: 'Limbic encephalitis' characterised by anterograde amnesia, seizures and psychiatric illness; 'Diencephalic encephalitis' characterised by somnolence and hypothalamic-pituitary dysfunction; 'Striatal encephalitis' characterised by movement disorders (parkinsonism, dystonia, chorea) and psychiatric features (attention deficit, emotional lability, obsessive-compulsive disorder, psychosis); 'Brainstem encephalitis' characterised by cranial neuropathies, ophthalmoparesis, parkinsonism, dysarthria or dysphagia and cerebellar ataxia[12]. Progressive cerebellar ataxia, dysphagia, pyramidal signs and behavioural changes were suggestive of brain stem encephalitis in our case.

A large number of antibodies have been described in association with AME. 'Brainstem encephalitis' is most commonly associated with anti-Ma2 antibodies in young men with testicular cancer but can also be caused by anti-Hu and anti-Ri antibodies[13,14]. AME cases without any detectable antibodies in the serum or CSF have also been reported in literature and termed as 'seronegative autoimmune encephalitis'. Most of these cases had a clinical and radiological picture suggestive of limbic encephalitis, with a negative infectious diseases workup and responded to immunotherapy and were therefore classified under the rubric of "Seronegative Limbic encephalitis"[15]. Similarly rare cases of 'brainstem encephalitis without antibodies' have also been described in literature and our case probably falls into this category. It is possible that these cases may be associated with antibodies directed against hitherto unrecognised new cell-membrane antigens undetectable by conventional immunohistochemistry. AME should be strongly suspected in patients presenting with acute or subacute, progressive or a relapsing-remitting encephalopathy developing over a period of weeks to months, as was the case with our patient. Diverse and multifocal neurological manifestations and a personal or family history of autoimmunity or seropositivity for organ-specific, systemic or neural-specific autoantibodies or an underlying cancer offer clues to the diagnosis. Subjective and objective evidence of clinical improvement following a 4 to 8 weeks trial of immunotherapy, serves as a valuable "diagnostic test" for confirming the diagnosis of AME as was also observed on our case.

AME can be associated with an underlying malignancy in up to 25% of cases[16]. Primary screening should therefore include: CT chest, abdomen and pelvis in all patients, mammography in women and testicular ultrasound and prostate-specific antigen (PSA) in men. If primary screening is negative, repeat screening should be performed every 3 - 6 months periodically, till up to 5 years[17]. Whole-body PET (FDG-PET) or combined CT/FDG-PET increases the cancer diagnostic yield by up to 20% and should be done in all cases with a high suspicion of a paraneoplastic syndrome[18]. In our case, even 2 years after the disease onset, screening for an occult malignancy was negative. Moreover, a good response to steroids argues against a paraneoplastic aetiology in our patient.

All cases with a diagnosis of AME warrant a trial of immunotherapy. The acute therapeutic phase serves as a diagnostic test as well and can include a trial of high dose pulse IV corticosteroids, intravenous Immunoglobulin (particularly in diabetics and those who cannot tolerate corticosteroids) and plasma exchange (generally reserved for critically ill patients). The response to immunotherapy is variable and significant predictors for improvement include: a subacute onset, fluctuating course, shorter delay to treatment, presence of non-neural specific and cell surface antibodies. In general AME associated with malignancies is less responsive to immunotherapy. A subacute onset encephalopathy without any evidence of underlying malignancy can be regarded as positive predictors of a favorable response to immunotherapy in our case. Relapses following steroid withdrawal are common and all patients with an initial good response should be considered for long-term maintenance immunosuppressive therapy, as was the case with our patient also. There is no consensus on the duration of immunosuppressive therapy but chronic

suppressive therapies include: oral steroids with or without a steroid sparing agent (azathioprine, mycophenolate mofetil and methotrexate) or weekly pulse doses of methylprednisolone or IVIG with subsequent tapering. Periodic attempts to withdraw immunosuppression should be made every 2 - 3 years since some patients may experience spontaneous remissions while others may require lifelong therapy. A brain biopsy should be considered in patients with a high level of suspicion for AME but lack of response to immunotherapy. Some patients with biopsy proven AME have shown a meaningful response to immunosuppressive therapy, only after a longer-term trial[19].

Table I: Causes of brainstem encephalitis.

Infectious

- Enteroviruses: Enterovirus 71, Poliovirus, Coxsackievirus A16, Echovirus
- Flaviviruses: Japanese encephalitis, St. Louis encephalitis, West Nile virus
- Herpes viruses: HSV, EBV, HH6, CMV, VZV
- Bacterial: Listeria, TB, Pneumococcus, Brucella, Borrelia (Lyme disease), Salmonella, Legionella, Mycoplasma
- Fungal and parasitic: Melioidosis, Aspergillus, Mucormycosis, Nocardia, Cysticercosis, Toxoplasmosis

Autoimmune

- Behcet disease/Relapsing polychondritis/SLE/Sjogren Syndrome/Multiple Sclerosis/Site restricted ADEM/ Bickerstaff Brainstem Encephalitis/Fischer Syndrome/ Vogt-Koyanagi-Harada Syndrome/Autoimmune or Antibody Mediated Encephalitis: Paraneoplastic or non-paraneoplastic

Neoplastic

- Lymphomas/Carcinomatous meningo-encephalitis

In conclusion, brainstem encephalitis can be caused by various infectious, neoplastic and autoimmune disorders. Non-vasculitic immune mediated causes of brainstem encephalitis include: site restricted ADEM, Bickerstaff brainstem encephalitis and AME. AME can be associated with systemic autoimmune disorders or can be paraneoplastic in nature. It can present as an acute or subacute, progressive or a relapsing-remitting encephalopathy with multifocal neurological manifestations. The radiological features and CSF findings are non-specific and AME remains a diagnosis of exclusion. Non-neural and neural specific autoantibodies in serum or CSF support the diagnosis of AME but seronegative cases have also been described and pose a diagnostic challenge. All cases with suspected AME should be given an empirical trial of immune-suppressive therapy and responders considered for long-term maintenance immunotherapy to prevent relapses following steroid withdrawal.

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PICTORIAL CME

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Tuberous Sclerosis Presenting as Gross Painless Haematuria

*Prabhat Kumar**

A 35-year-old male patient presented to the emergency department with complaints of gross haematuria for the last 2 days which was not associated with any fever, pain or trauma. There was no significant past history. On examination, he had facial angiofibromas (Fig. 1), shagreen patch on trunk (Fig. 2) and hypopigmented macules on abdomen (Fig. 3). Fundus examination showed hamartomas in right eye. His vitals were stable and bilateral kidney were enlarged and ballotable. Blood investigations showed anaemia with a Hb of 7gm/dl and mildly deranged renal parameters (urea - 56 mg/dl and creatinine - 1.5 mg/dl). Ultrasound abdomen revealed bilaterally enlarged kidneys (size approximately 18 cm) with deformed echotexture and irregular margins. There were multiple hypoechoic masses measuring 1 cm to 8 cm in both kidneys. There was a hyperechoic hematoma in urinary bladder of size 10 cm x 7 cm. CECT abdomen showed bilaterally enlarged kidneys with lobulated margins and areas of fat attenuation within. Non contrast images showed few hyperdense mass lesions (largest measuring 7 x 5 x 3.5 cm on right side and 2 x 1.4 x 2.8 cm on left side) which showed post-contrast enhancement suggestive of angiomyolipomas. There was evidence of a nonenhancing mobile mass in urinary bladder suggestive of hematoma (Figs. 4, 5). Non contrast CT of head showed subependymal nodules (Fig. 6). He was transferred to department of urology where he underwent renal artery embolisation for ongoing bleeding.

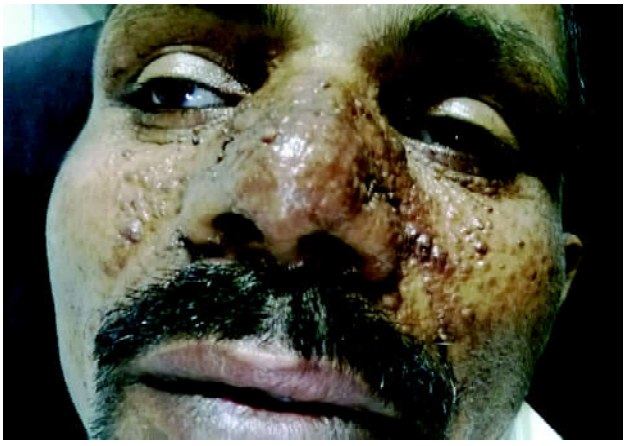

Fig. 1: *Facial angiofibromas.*

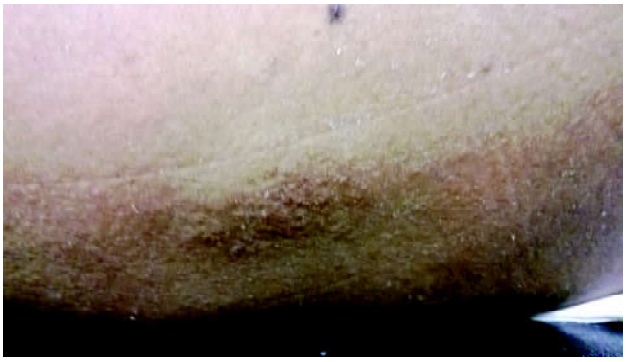

Fig. 2: *Shagreen patch on trunk.*

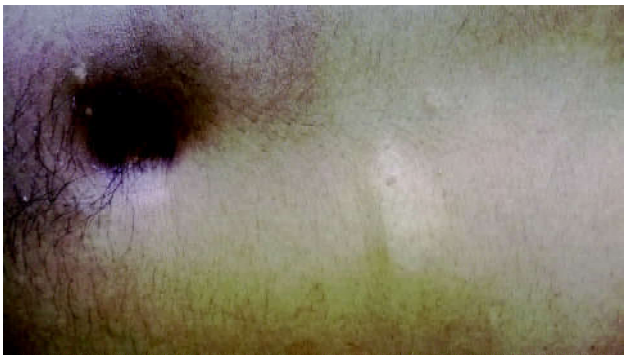

Fig. 3: *Multiple hypopigmented (Ash Leaf) macules on abdomen.*

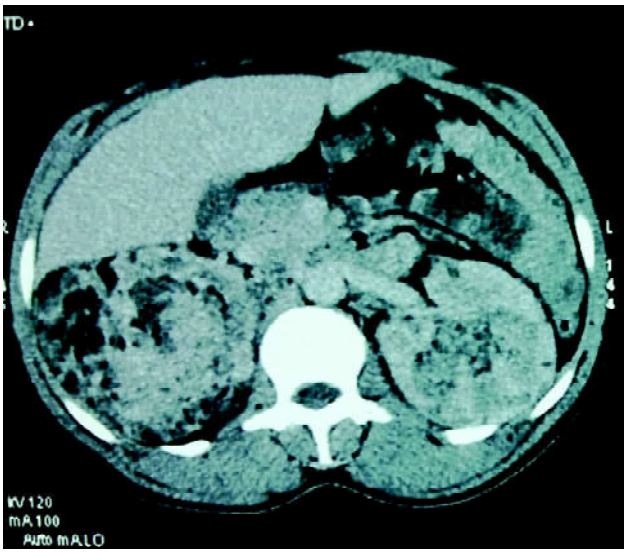

Fig. 4: *CECT abdomen showing bilaterally enlarged kidneys with mass lesion.*

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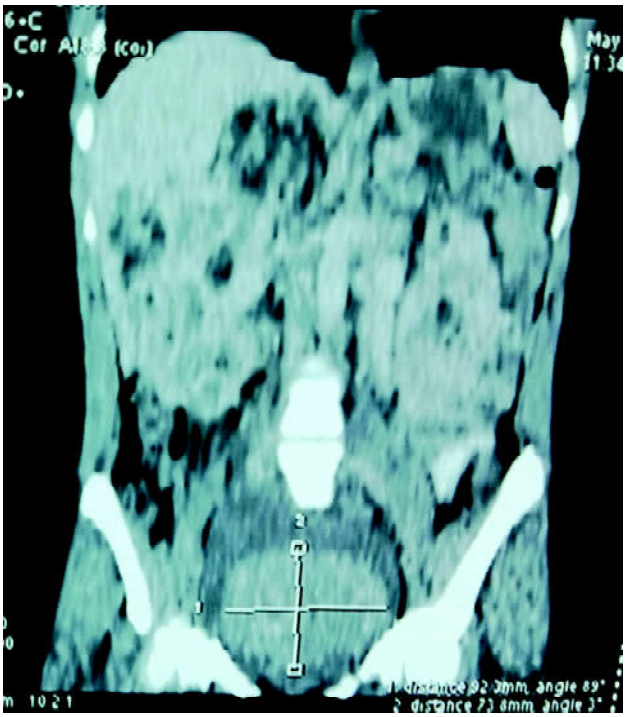

Fig. 5: *CECT showing grossly enlarged kidneys with haematoma in the urinary bladder.*

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with an incidence of approximately 1 in 5,000 to 10,000 live births. It is characterised by presence of hamartomas in various organs of body such as brain, kidney, lung, skin, heart and eye.

The clinical triad includes mental retardation, seizures, and facial angiofibromas[1]. Angiomyolipomas (AMLs) and renal cysts are the common renal anomalies in TSC. Incidence of renal AML is 50 - 80% and that of cyst is about 18 - 53% and for both is 12 - 27%[2-4].

Diagnosis is made by genetic and clinical criteria. Clinical criteria for tuberous sclerosis has 11 major features (hypomelanotic macules, angiofibromas, ungual fibroma, shagreen patch, multiple retinal hamartomas, cortical dysplasias, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, angiomyolipomas) and 6 minor features (confetti skin lesions, dental enamel pits, intraoral fibromas, retinal achromic patch, multiple renal cysts, nonrenal hamartomas). For definite diagnosis two major features or one major and two or more minor features are needed.

The patient had no neurological symptoms and none of his family members had similar disease. Late presentation with only hematuria is unusual with only few reported cases.

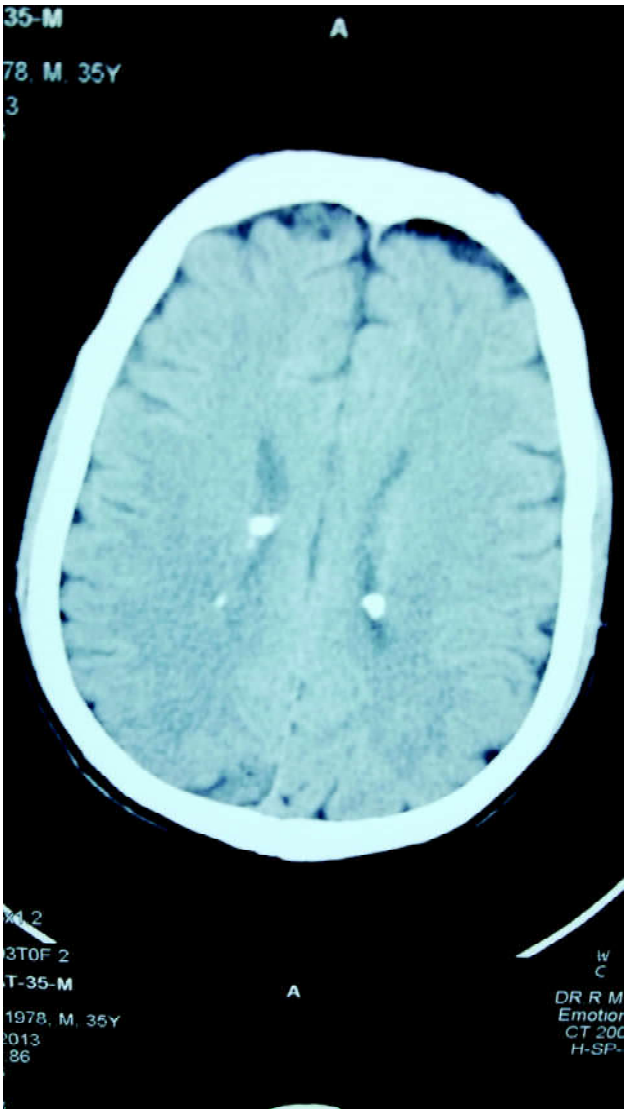

Fig. 6: *NCCT head showing subependymal nodules.*

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