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VIEWPOINT

JIACM 2015; 16(1): 6-8

From ignorance through science to wisdom

*BM Hegde**

"The only true wisdom is in knowing you know nothing."

– Socrates.

One of my e-mail patients, Jayashree Nair, sent me a few quotes from Aurobindo, one of our venerated sages. Some of them beat even the latest quantum physics dictates. I shall quote some of them for the reader's benefit and then we shall debate the significance of ignorance, science, and wisdom in that order. I shall also quote some of the celebrated scientists, most of them Nobel recipients, to buttress the argument for a connection between all these three, more for the benefit of the RNI (resident non-Indian) thinkers here.

Ignorance

Ignorance, they say, is bliss. This might have been a superstition but it is true in today's medical world which has become a "corporate monstrosity" and the claptrap there will confuse the best brains to make them hypochondriacs. As Richard Feynman, a Nobel physicist said "The first principle is that you must not fool yourself – and you are the easiest person to fool." In today's environment if you try to find out something about disease and its remedies, you will soon be fooled. The medical world has found millions of ways to confuse and trap you in their net. Lay people think that they are ignorant about that hallowed word "science"; the very mention of the word makes even cow dung become a medicine. The food industry uses this trick to sell their dangerous junk foods as scientifically proven for this or that disease! The higher you go up the conventional schooling system, the bigger is your ego to eat only scientifically proven healthy food and scientifically proven other methods of lifestyle.

What is this "science"? Definitions vary from such simple ones like "science is measurement and measurement is science" by Marie Curie to such complicated ones like: "science is the belief in the ignorance of experts..." by Richard Feynman. There again ignorance raises its ugly head. The best assessment of science was done by Aurobindo during his time. "Medical Science has been more of a curse to mankind than a blessing. It has broken the force of epidemics and unveiled a marvellous surgery; but, also, it has weakened the natural health of man and multiplied individual diseases; it has implanted fear and dependence in the mind and body; it has taught our health to repose not on natural soundness but a rickety and distasteful crutch compact from the mineral and vegetable kingdoms." How true?

A very recent study in four universities – Oxford, Cambridge, Hamburg, and Munich – clearly showed that it is the 'Placebo effect', the faith of the patient in the doctor and his medicines, that heals. This study was led by Professor Bingel of Oxford University. Look at what Aurobindo has to say about faith and its role in healing? "We laugh at the savage for his faith in the medicine man; *but how are the civilised less superstitious who have faith in the doctors?* The savage finds that when a certain incantation is repeated, he often recovers from a certain disease; he believes. The civilised patient finds that when he doses himself according to a certain prescription, he often recovers from a certain disease; he believes. Where is the difference? *One could say in conclusion that it is the faith of the patient which gives the remedy its power to heal.* If men had an absolute faith in the healing power of Grace, they would perhaps avoid many illnesses."

In his recent TED talk Mark Plotkin, an ethnobotanist, brings out this remarkable truth which tells us that the best science is yet to be discovered! "The greatest and most endangered species in the Amazon rainforest is not the jaguar or the harpy eagle. It's the isolated and uncontacted tribes." He brings us into the world of the "forest's indigenous tribes and the incredible medicinal plants that their shamans use to heal. He describes the "challenges and perils" that endanger them. He rightly urges the world to protect this irreplaceable repository of wisdom.

Now let me ask the reader which one of these is science and which superstition? Aurobindo goes on to add that the "healthiest ages of mankind were those in which there were the fewest material remedies. We ought to use the divine health in us to cure and prevent diseases; but Galen and Hippocrates and their tribe have given us instead an armoury of drugs and a barbarous Latin hocus-pocus as

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our physical gospel."

Science and knowledge

"*Science is simply making models, mathematical constructs, which with verbal jargon are supposed to work,*" wrote John von Newman, a Hungarian born American Nobel-winning chemist! Consequently, science is another one of those human enterprises, like religion, which has its inbuilt limitations. Peter Medawar, another Nobel Laureate medical scientist in his classic *The Limits of Science* goes on to say that science is designed for some limited purpose and thus can answer mundane questions. When it comes to esoteric questions like origin of life or of this world, the nature of God and end of life, etc., science is powerless to answer! His analogy is very telling. Science is built like a railway engine and if asked to fly like an aeroplane it naturally fails to do so, he adds. Being a venerated scientist, he hastens to add that his statement should not be misconstrued as to mean that science is powerless. He feels science has served its purpose very well. I beg to differ there. Science, which has now tagged itself on to technology, is today running after big money and, therefore, has lost its way. Money runs science and research today to the detriment of the humanity's needs. Many of the technologies are killer technologies says a friend of mine, a distinguished BARC nuclear scientist. Positive sciences have become so reductionist that they cannot look at the whole at all. Reductionist science, nay vivisectionist science, brings in money for the industry and, as such, is being patronised by the money bags with liberal grants, expecting something in return. The research, thus, becomes subservient to grant givers' interests. Today's big scientists are those that succeed in getting the largest grants and then producing scientific papers like the magician bringing out pigeons from his hat, fattening his/her CV. Of course, prizes and awards are an added attraction.

Science must basically be the curiosity to try and understand nature. Lately, thanks to technology, science took on itself the role of teaching nature a lesson or two. That is where it got derailed completely. The science of genetics went on to teach human genes some tricks to make money in the name of genetic engineering, stem cell research, cloning, producing self-replicating nanobots to beget offsprings without parents, etc. Similarly in physics billions of dollars are being wasted to find out the basic building particles of this universe, the so called Goddem or God particle, the Higg's Boson. About a year ago when the last grant amount was coming to an end at the CERN reactors, there appeared a flurry of news items about the foundation of the universe, the God particle being discovered with almost 99.9% certainty. Now it is forgotten and no one talks about it. Are there particles at all? Human memory being short people forgot about that particle. The only certainty in this universe is uncertainty, thanks to Werner Heisenberg who discovered it in 1925 through Gedanken experiment – a thought experiment – in the best laboratory in the world, the human mind. Science is ceaseless change like life itself. So there is nothing called *THE TRUTH* in science. There could be *A TRUTH* at a given time. If science finds its Holy Grail, there will be no more enterprise called science. Science, therefore, is not the end in itself. It is knowledge and so is very proud and arrogant because it knows so much! Science dwells in heads replete with thoughts of other men, books, journals, and what have you; rarely does it dwell in heads attentive to their own...

Wisdom

Wisdom, on the contrary, is humble as it knows no more. Many great scientists have become wiser at the end of the day and have reached similar conclusions that Sri Aurobindo preached from the internal engineering of his mind. Science has made the external world to progress at breakneck speed with highways, rockets, landings on the moon and mars, organ transplants, vertical living facilities, bombs, terrorists, submarines, planes, and more – thanks to its arrogance of success it seems to think that it can even teach nature some lessons. Life on earth though has become very difficult these days with human atrocities against fellow humans in all spheres of activity from economics, health, governance, and what have you. Little do we realise that the basic principle of life on earth is its interconnectedness. The "I" (illness) concept has taken over from the more natural "we" (wellness) concept to end this world sooner than later. Materialism has replaced spirituality in every walk of life. William Wordsworth, that romantic British poet, wrote as far back as 1802 in his poem, *The World Is Too Much With Us,* that we have sold our soul, (to the Devil) a sordid boon. If mankind has to survive here, we need to re-engineer our inner development with wisdom and spirituality. The simple meaning of spirituality is simple sharing and caring. That needs wisdom.

Science also has revealed an astonishing interconnectedness of things, starting with Newton's principle of universal gravitation, where all bodies in the universe influence one another. The field theories, evolutionary theory, quantum physics, Gaia theory, and modern cosmology, new principles of interconnectedness, if understood properly with humility, seem to link separate systems into a larger whole. Some sagely thinkers in science, like Sri Aurobindo, seem to go a bit too far to reveal previously unsuspected links between the realms of the

subjective and objective. Mind is not just confined to the human brain but is a part of the universal consciousness. May be the minds can connect the present with the past. What looks on the surface to be a duality is in fact, at a deeper level, non-dual. Non-dualism, which he compares with *Advaita*, is at the core of the thinking of one of the leading living sages of science, Hans Peter Durr, emeritus director of the Max Planck Institute in Munich.

Reality in the true sense, according to quantum laws, is not something we can touch and comprehend. We can comprehend much more than we can grasp. Reality is an "immaterial wholeness 'Gestalt', pure interconnectedness, inseparable potentiality, comparable to the mental sphere," feels Hans Peter Durr. It corresponds to a holistic and unified process of action. Paul Brunton, a British philosopher, mystic and a traveller, wrote that: "I knew however that the forest thinkers of Asiaitic countries had leisurely pondered this problem long before the first city Greeks had begun to ponder it in Europe. Moreover, there was this vital difference that whereas the Western thinkers usually claimed that nobody had discovered ultimate truth and that human limitations were so narrow that nobody was likely to discover it, the authors of old Asiatic books (*Indian Sages*) claimed that ultimate truth was certainly discoverable and that a few sages had definitely known it. Even an erudite quantum physicist like Erwin Schrodinger feels that: "the multiplicity is only apparent. This is the doctrine of the Upanishads. And not of the Upanishads only. The mystical experience of the union with God regularly leads to this view, unless strong prejudices stand in the West." Ramana Maharishi, a great Indian sage had this to say about the "I" concept referred to above:

"Sooner or later the question of 'Who am I' will have to be faced. All [practice] that leads to this question is good. For, by itself, nothing else is fully effective since Self-knowledge comes only through Self-Inquiry. Other methods purify the mind and help it to see its own limits. When the mind comes to the end of its resources, and stands baffled before the unanswerable question, then a Higher Power takes charge of the mind and the Self stands revealed as the real, the wonderful."

One can feel the oneness between the East and West when one is able to go into the human mind. I strongly feel that Rudyard Kipling was wrong when he wrote that "the East is east and the West is west; the Twain shall never meet." I would have modified it thus for the good of mankind as we have seen above: The East is east and the West is west, but it will be the BEST when they both meet. This new wisdom if put into practice can send all of us to our neighbours' houses with a broad smile on our face to have a cup of tea instead of sending terrorists to blast their homes and try to send man to moon instead as we are likely to raze all "homes" to the ground with our hatred and jealousy. Wisdom will make us tranquil and feel one with others, the ultimate need of the hour for the survival of our race on this planet, which is true even in quantum physics. Science becomes wisdom when the arrogant scientist realises that he is not omnipotent. The common saying goes thus: "A wise man knows he is a fool while a fool always thinks that he is wise."

"Do not go where the path may lead, go instead where there is no path and leave a trail."

– Ralph Waldo Emerson.

"Do not resent growing old...
Many are denied the privilege."

– Old Irish Proverb.

ORIGINAL ARTICLE

JIACM 2015; 16(1): 9-11

Should patients with inferior, posterior, and right ventricular infarction be thrombolysed?

SH Verma, YB Agarwal*, SK Sharma*, RK Pandey*, P Subodh**

Abstract

The objective of this study was to compare the effects of thrombolysis on acute cardiac events, ECG on admission and in-hospital mortality in the patients of acute inferior, posterior, and right ventricular myocardial infarction. The study included 50 patients of acute inferior (56%), inferior with posterior (22%), inferior with right (10%) and inferior with right and posterior ventricular infarction (12%). The mean age of the patients was 54 yrs, and the male: female ratio was of 4.5: 1.

Group A (56%) were thrombolysed and group B (44%) not thrombolysed, as they had contra-indications for therapy. Before thrombolysis, mean duration of chest pain was 4.2 ± 2.0 hrs. in group A and 21.2 ± 4.6 hrs. in group B. On admission, q waves were present in 25% of group A and 95.4% of group B. Group A had mean ST elevation of 4.2 ± 2.05 while group B of 2.95 ± 1.7 mm. Conduction defects observed were I° AV block in 14.2% (group A), 13.6% (group B), II° AV block in 3.5% (group A), and complete heart block in 27% of group B. Mean duration for chest pain to subside was 9.14 ± 3.02 hrs. in group A, and 10.18 ± 3.19 hrs in group B. Mean time for ST segment to normalise was 3.45 ± 1.85 days in group A, and 5.09 ± 2.25 days in group B. Re-infarction was more common in group B as compared to group A (13.6% Vs 7%). Seventeen per cent of group A had post-infarction angina as compared to 4.5% of group B and 4.5% of group B had asystole. Hypotension, congestive cardiac failure, II° AV block, complete heart block, and ventricular tachycardia were more common in group B as compared to group A. (36% vs 7.1%, 13.6% vs 10%, 13.6% vs 3.5%, 27.2% vs 7% and 9% vs 3% respectively. After thrombolysis, complications like haemorrhagic stroke and haematemesis occurred in one patient each. It was observed that in-hospital complications and overall mortality was more in group B as compared to group A (54% vs 17.8%). Therefore, it is recommended that even inferior myocardial infarction should be thrombolysed.

Key words: Inferior, right ventricular, posterior myocardial infarction, thromolysis.

Introduction

Inferior wall myocardial infarction usually has a better prognosis than anterior myocardial infarction[1]. Patients with inferior myocardial infarction who might have otherwise be considered to have a low risk of mortality and for whom many physicians have questioned the benefits of thrombolytic therapy, might be in a much higher mortality risk group, if their inferior infarction is associated with right ventricular infarction, precordial ST segment depression or ST segment elevation in the lateral precordial leads[2]. Pooled data of the recent studies of inferior wall myocardial infarction indicate that both mortality rates and in-hospital complication rates increased markedly in the 60% to 80% of the patients not suitable for thrombolytic therapy[3].

Aims and objectives

To compare the effects of thrombolysis on acute events, ECG on admission and in-hospital mortality in the patients of acute inferior, posterior, and right myocardial infarction.

Material and methods

Fifty patients of acute inferior, posterior, and right ventricular infarction admitted to ICCU were included in the study. Acute inferior myocardial infarction was diagnosed by typical chest pain lasting for more than 30 minutes, ST segment elevation of $\geq$ 1 mm in two of the leads, right ventricular infarction by ST segment elevation of $\geq$ 1 mm in V_3R and V_4R and posterior infarction by tall T in V_2V_3 and raised CPK (MB) levels.

The patients were of either sex between the age group of 31 - 90 yrs. Detailed history of each patient was obtained. Thorough physical systemic examination was done. The patients were divided into two groups, groups A included the patients who received thrombolytic therapy in the form of intravenous streptokinase 1.5 million units; and group B, who did not receive thrombolytic therapy.

Serial ECGs were recorded just before giving STK, and 30 minutes, 6 hours, 12 hours, and 24 hours after administration of STK. Later, daily ECGs were recorded till patients remained in ICCU or expired.

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Results

The study included 50 patients of acute inferior (56%), inferior with posterior (22%), inferior with right (10%) and inferior with right and posterior ventricular infarction (12%). Table I shows the percentages of acute myocardial infarction. The mean age of 4.5: 1. Fifty-six per cent were thrombolysed and forty-four per cent were not thrombolysed. Groups A had a mean age of 55.4 yrs and male: female ratio of 3.6: 1; group B had a mean age of 58.1 yrs and male: female ration of 6.3 :1.

Before thrombolysis, the mean duration of chest pain was 4.2 ± 2.0 hrs in group A, and 21.2 ± 4.6 hrs in group B. On admission, q waves were present in 25% of group A and 95.4% of group B. Group A had mean ST elevation of 4.2 ± 2.05 while group B of 2.95 ± 1.7 mm. Conduction defects like I° AV and II° AV blocks were more common in group A as compared to group B. 14.2% vs 13.6% and 3.5% vs nil respectively. Complete heart block (27%) was observed only in group B on admission (Table II).

The mean time for chest pain to subside was 9.14 ± 3.02 hrs in group A, and 10.18 ± 3.19 hrs in group B. The mean time for ST segment to normalise was 3.45 ± 1.85 days in group A, and 5.09 ± 2.25 days in group B.

Re-infarction was more common in group B as compared to group A (13.6% vs 7%). Seventeen per cent of group A had post-infarction angina as compared to 4.5% of group B, and 4.5% of group B had asystole. Hypotension, congestive cardiac failure, II° AV block, complete heart block and ventricular tachycardia were more common in group B as compared to group A. (36% vs 7.1%, 13.6% vs 10%, 13.6% vs 3.5%, 27.2% vs 7% and 9% vs 3% respectively. The mean duration of hospital stay was 10.67± 3.26 days in group A, and 6.39 ± 2.52 days in group B – probably because mortality was more in group B. After thrombolysis, complications like haemorrhagic stroke and haematemesis occurred in one patient each of group A. Re-perfusion arrhythmia occurred in only one patient of group A (Table III).

Table I: Shows % of acute inferior, posterior, and right ventricular myocardial infarction.

S.No.	Types of infarction	Group A (n = 28)	Group B (n = 22)	Total
1.	Inferior	19(67.8%)	9(40.9%)	28(56%)
2.	Inferior + posterior	7(25%)	4(18.18%)	11(22%)
3.	Inferior + right	1(3.57%)	4(18.18%)	5(10%)
4.	Inferior + right + posterior	1(3.57%)	5(22.7%)	6(12%)
	Total	28(56%)	22(44%)	50(100%)

Table II: Shows ECG on admission in group A and B.

S.No	ECG on admission	A (n = 28)	B (n = 22)
1.	q waves		
	• present	7(25%)	21(95.4%)
	• absent	21(75%)	1(4.5%)
2.	Mean ST elevation	4.2 ± 2.05	2.95 ± 1.7 mm
3.	Conduction defects		
	• I°AV block	4(14.2%)	3(13.6%)
	• II°AV block	1(3.57%)	Nil
	• Complete heart block	Nil	6(27.2%)

Table III: Comparison of prognostic indicators in thrombolysed vs non-thrombolysed.

S.No.	Prognostic indicators	A (n = 28)	B (n = 22)
1.	Mean time for chest pain to subside in hrs	9.14 ± 3.02	10.18 ± 3.19
2.	Mean time for ST segment to normalise	3.45 + 1.85	5.09 + 2.25
3.	In-hospital complications		
	• I°AV block	3(10.7%)	1(4.7%)
	• II°AV block	1(3.5%)	3(13.6%)
	• Complete heart block	2(7%)	6(27.2%)
	• Ventricular tachycardia	1(3%)	2(9%)
	• Hypotension	2(7.1%)	8
	• Congestive cardiac failure	3(10%)	3(13.6%)
	• Post-infarction angina	5(17.8%)	1(4.5%)
	• Asystole	Nil	1(4.5%)
4.	Mean duration of hospital stay in days	10.67 ± 3.26	6.39 ± 2.52
5.	Mortality	5(17.8%).	12(54%)

Discussion

The prognosis is better in inferior wall myocardial infarction as compared to anterior myocardial infarction. Patients with inferior myocardial infarction have a low risk of mortality and therefore many physicians have questioned the benefits of thrombolytic therapy. Our study was undertaken to determine the benefits of thrombolytic therapy in patients with acute inferior myocardial infarction with or without right ventricular and posterior myocardial infarction. A similar study by other researchers has found right ventricular involvement commonly complicates acute inferior myocardial infarction and benefits most from thrombolytic therapy[4]. We studied 50 patients of acute inferior wall myocardial infarction; 56% had inferior, and 12% had inferior with right and posterior venricular infarction which is comparable to another study where 47.33% had inferior wall infarction. 13.34% had associated right ventricular and posterior infarction[5]. In our study, before thrombolysis, the mean duration of chest pain was 4.2 ± 2.0 hrs in group A and 21.2 ± 4.6 hrs in group B. On

admission, q waves were present in 25% of group A, and 95.4% of group B – because group B patients took more time to seek medical treatment from the onset of symptoms. A study by Achari *et al*[5] reported the mean onset of symptoms and hospital admission was 20.6 ± 8.0 hrs in patients who were not thrombolysed.

In our study, the overall in-hospital complications in acute inferior myocardial infarction were more in non-thrombolysed group as compared to thrombolysed group (67.5% vs 46.3%). Similarly, a study by Zehender *et al*[4] reported more in-hospital complications in non-thrombolysed patients (56% vs 31%). In the pre-thrombolytic era, second or third degree AV nodal blocks were seen in 28% of inferior wall myocardial infarction[6]. In our study, II° AV nodal block was present in 13.6%, and complete heart block in in 27.2% of patients who did not receive thrombolytic therapy. One study by Pirzada *et al*[7] reported II° AV nodal block in 1.5%, and complete heart block in 16% after acute inferior wall myocardial infarction who received thrombolytic therapy. Our study has shown II° AV nodal block in 3.5%, and complete heart block in 7% of patients with inferior myocardial infarction who were thrombolysed. In one study by Garcia *et al*[8] it is mentioned that thrombolytic therapy is most efficient in reversión of complete atrioventricular block. In our study also, complete heart block reverted back to normal sinus rhythm in all the patients who were thrombolysed.

Comlications like congestive cardiac failure, post-infarction angina and cardiac asystole were found in 13.6%, 4.5% and 4.5% of non-thrombolysed group respectively in our study. Another study showed similar complications in 10%, 28%, and 10% of non-thrombolysed patients respectively[9]. Mortality was significantly higher in non-thrombolysed patients as compared to thrombolysed patients (54% vs 17%) in our study. Other reserachers also reported more mortality in non-thrombolysed patients of acute inferior myocardial infarction (25% vs 8%)[4].

Conclusions

Fifty patients of acute inferior, posterior, and right ventricular infarction with a mean age of 54 yrs and male: female ratio of 4.5: 1 were studied. Duration of chest pain was less, and ST segment elevation was more, in the thrombolysed patients. Q waves, II° AV block, and complete heart block were frequently seen in the patients who were not thrombolysed. ST segment normalises earlier in thromblysed patients. In-hospital complications like re-infarction, asystole, congestive cardiac failure, ventricular tachycardia were more in patients who were not thrombolysed.

Hence it is concluded that the clinical course of acute inferior wall myocardial infarction is favourably affected by thrombolytic therapy and this study recommends thrombolytic therapy even in inferior wall myocardial infarction, more so when it is associated right ventricular and posterior wall infarction.

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"Perseverance will prevail where all others will fail."

– Anonymous.

ORIGINAL ARTICLE

JIACM 2015; 16(1): 12-5

To study the association of high sensitivity C-reactive protein with newly diagnosed DM type 2

Abha Gupta, Dilip Kumar**, Satyam Rajvanshi**, Arvind Kumar***, TVS Arya*****

Abstract

Introduction: *C-reactive protein is an acute phase response protein markedly increased in both inflammatory and infectious diseases. It is an established risk marker for cardiovascular diseases and rheumatic diseases. Recent prospective studies have suggested that an elevated level of CRP is associated with an increased risk of developing type 2 diabetes. The present study was conducted with the objective of studying the association of hs-CRP with newly diagnosed diabetes mellitus type 2.*

Material and methods: *A total of 110 subjects were divided into newly diagnosed diabetic patients (group A with 54 subjects; 32 males, 22 females) and healthy controls (group B with 56 subjects; 33 males, 23 females). Cross-sectional analysis of anthropometric and biochemical parameters like BMI, fasting and post-prandial plasma glucose, lipid profile, and hs-CRP was carried-out in both groups. Association of hs-CRP with these parameters was studied using appropriate statistical tests.*

Results: *Mean hs-CRP in group A (4.07 ± 1.96) was found to be significantly higher than group B (1.59 ± 0.86, $p < 0.05$). Mean hs-CRP of females in both groups was significantly higher than males (4.68 ± 1.80 vs 3.64 ± 1.97 in group A; and 2.14 ± 0.78 vs 1.20 ± 0.70 in group B respectively, $p < 0.05$). The higher levels of hs-CRP were found to be significantly associated with age, fasting blood sugar, HbA1C level, BMI, total cholesterol, HDL, LDL, and triglyceride levels.*

Conclusion: *We concluded that higher levels of hs-CRP can be a predictive factor for the development of type 2 DM. It also has positive correlation with HbA1c, reflecting the glycaemic status of the patient. This study also suggests that a proper planning to monitor complications of artherosclerosis among diabetic patients can be done by measuring the concentration of plasma hs-CRP in addition to other recommended biochemical parameters.*

Keywords: *hsCRP, DM type 2, inflammation.*

Introduction

There has been an increasing interest in the involvement of low grade inflammation in the pathogenesis of type 2 diabetes[1]. C-reactive protein (CRP) is an inflammatory marker produced and released by the liver under the stimulation of cytokines such as tumour necrosis factor-α and interleukins 1 and 6. It affects the process of atherothrombosis[2,3], hence has emerged as a powerful risk marker for cardiovascular disease[4-6]. Inflammation has also been postulated to play a role in the pathogenesis of type 2 diabetes. Recent prospective studies have suggested that an elevated level of CRP is associated with an increased risk of developing type 2 diabetes[7-10]. Some of the risk may be mediated through obesity and factors related to insulin resistance[9]. CRP has received the most attention as a marker of inflammation in both rheumatic and non-rheumatic disease. CRP can rise as high as 1,000-fold with inflammation. Conditions that commonly lead to marked changes in CRP include infection, trauma, surgery, burns, inflammatory conditions, and advanced cancer. Moderate changes occur after strenuous exercise, heatstroke, and childbirth. Small changes occur after psychological stress and in several psychiatric illnesses.

The present study was conducted at LLRM Medical College and associated SVBP Hospital, Meerut, with the objective of studying the association of high sensitivity-CRP (hs-CRP) with newly diagnosed diabetes mellitus type 2.

Materials and methods

This study was a cross-sectional study in which hs-CRP levels of patients of newly diagnosed DM type 2 (within six months) was compared with the controls. The controls were healthy individuals. The diagnosis of diabetes was made on the basis of clinical evaluation, biochemical and ancillary investigation like FBS/PPBS, HbA1c. A detailed clinical history with specific reference to CVS problems, drug intake, and smoking was taken. A complete general and systemic examination, particularly for stigmata of infection and cardiovascular status, was carried-out. Patients of both sexes between the ages of 30 to 60 years with newly diagnosed diabetes (within six months) were included. Patients with recent myocardial infarction, rheumatic fever, any inflammatory and other conditions which could alter CRP

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levels, and patients with primary cardiac disease, hypertension, renal failure, and pulmonary disease were excluded from this study. Subjects were divided into two groups. Group A comprised of cases (newly diagnosed diabetics), and group B comprised of controls (healthy non-diabetic individuals). The significance of the hs-CRP levels in newly diagnosed diabetics analysis were tested on various metabolic and biochemical parameters for 56 healthy non-diabetic subjects and 54 diabetic individuals. Anthropometric measurements and biochemical parameters like fasting and post-prandial plasma glucose, lipid profile, LFT, KFT and routine urine analysis were carried out. Statistical analysis was done by One Way ANOVA or Student 't' test as appropriate to compare groups for continuous variables. The Chi-square test or Fisher's exact test – as was deemed appropriate – was used to compare proportions. Pearson's correlation analysis was done to determine the relation of hs-CRP with other risk variables. All the analyses were done by using the Windows-based SPSS statistical package (version 15.0; SPSS Inc; Chicago, IL, USA) and p-values < 0.05 were taken as the level of significance.

Observations

In group A, out of total 54 patients, 32 (59.25%) were males and 22 (40.74%) were females; and in group B, there were 33 (58.92%) males and 23 (41.07%) females out of total 56 patients. All patients completed the study. Mean age of patients in group A was 49.13 ± 5.48 years, in group B was 49.41 ± 5.75 years.

Mean hs-CRP in group A was 4.07 ± 1.96% which is significantly (p < .001) higher than group B (1.59 ± 0.86) (Table I). Mean hs-CRP of females in group A and group B were significantly higher than males (p < .001) (Table I). Mean systolic and diastolic BP of group A was significantly (p < .001) higher than group B (Table II). Also, mean BMI of group A statistically higher than group B (25.51 ± 1.98 and 23.43 ± 2.27 respectively) (Table III). There was a trend towards higher mean total cholesterol and mean LDL in group A compared to group B (Table IV). It was found that higher levels of hs-CRP were positively associated (p < 0.05) with FBS, HbAIC levels, BMI, total cholesterol, LDL, triglyceride levels, higher values of systolic and diastolic BP and age. Hs-CRP was negatively associated with HDL levels (Table V, VI).

Table I: Mean hs-CRP in group A and group B.

S.No.	Group	Total no.	Males/ females	Mean hs-CRP (total)	Mean hs-CRP (males)	Mean hs-CRP (females)
1.	A	54	32/22	4.07 ± 1.96	3.64 ± 1.97	4.68 ± 1.80
2.	B	56	33/23	1.59 ± 0.86	1.20 ± 0.70	2.14 ± 0.73

Table II: Mean blood pressure in group A and group B.

S. No.	Group	No.	Mean SBP	Mean DBP
1.	A	54	130.52 ± 4.98	82.85 ± 2.90
2.	B	56	117.43 ± 6.83	77.43 ± 2.97

Table III: Mean BMI in group A and group B

S. No.	Group	No.	Mean BMI
1.	A	54	25.51 ± 1.98
2.	B	56	23.43 ± 2.27

Table IV: Mean lipid profile values in group A and group B.

S. No.	Parameter	Group A	Group B
1.	Total cholesterol	165.78 ± 20.30	159.16 ± 16.14
2.	Mean HDL	39.37 ± 4.57	39.27 ± 4.83
3.	Mean LDL	111.57 ± 15.06	107.75 ± 17.54
4.	Mean TG	144.70 ± 28.61	116.04 ± 21.95

Table V: Pearson correlation of hs-CRP with FBS, HbA1c, BMI, age.

S. No.	Correlate	Test	P-value
1.	FBS	0.66	< 0.05
2.	HbA1c	0.62	< 0.05
3.	BMI	0.60	< 0.05
4.	Age	0.46	< 0.05
5.	Systolic BP	0.58	< 0.05

Table VI: Pearson correlation of hs-CRP with total cholesterol, HDL, LDL and triglyceride levels.

S. No.	Correlate	Test	P-value
1.	Total cholesterol	0.66	< 0.05
2.	HDL	- 0.36	< 0.05
3.	LDL	0.70	< 0.05
4.	Triglyceride	0.51	< 0.05

Discussion

Diabetes is a metabolic disorder with inappropriate hyperglycaemia either due to an absolute or relative deficiency of insulin secretion, or reduction in the biologic effectiveness of insulin, or both. It is also associated with disturbances concerned with protein, carbohydrate, and lipid metabolism. CRP – a pentameric protein produced by the liver – has emerged as the 'golden marker for inflammation'. It is a non-immunoglobin protein having five identical sub-units. It

is a member of pentraxin family of proteins. It is an acute phase response protein markedly increased in both inflammatory and infectious diseases and plays an important role in innate immunity. It assists in complement binding to foreign and damaged cells and enhances phagocytosis[2]. Median level of hs-CRP in apparently healthy subjects is 0.8 mg/dl. Higher levels of hs-CRP are a marker of chronic inflammation in apparently normal healthy individuals. The assessment of atherosclerosis, which is a chronic inflammatory process from the very beginning, helps to calculate the risk of cardiovascular and cerebrovascular events in patients. Several studies demonstrate that hs-CRP remained a significant predictor of diabetes risk even after adjusting with body mass index, family history of diabetes mellitus, smoking, and other factors[6]. In people with diabetes, high CRP levels (> 0.8 mg/dl) were associated with a two-fold increase in CV mortality after adjusting for age, sex, and glucose tolerance tests[9-11]. Studies on western populations have shown low grade systemic inflammation to be one of the mechanisms by which known risk factors such as obesity, smoking, and hypertension promote the development of diabetes mellitus[6,13]. However, there are few studies of hs-CRP in Asian Indians, a very high-risk group for diabetes[14-16]. The hs-CRP seems to be strongly associated with diabetes mellitus and insulin resistance. Several studies done earlier have also shown that hs-CRP predicts diabetes in western populations[6,17,18] as a biomarker of inflammation. Another observation was the relationship of hs-CRP with glycaemic control. A prospective study on the type 2 diabetic subjects suggested a decrease in hs-CRP levels with a decrease in HbA1c and higher values of hs-CRP are also associated with fasting hyperglycaemia[19]. A recent population based study showed hs-CRP to be independently associated with fasting plasma glucose[20]. Though we have several studies on hs-CRP and diabetes mellitus, association with newly diagnosed diabetes is limited. Therefore the current study focussed on the association of hs-CRP and newly diagnosed diabetes mellitus. In the present study, we found that the median hs-CRP levels were significantly higher in both diabetic men and women as compared to their non-diabetic counterparts. Subjects with higher hs-CRP had higher proportion of hypertensives, obese, and hyper-cholesterolaemic patients. Higher hs-CRP was also positively correlated with higher HbAIC and fasting hyperglycaemia.

Conclusion

We demonstrated the significant association of low grade inflammation as indicated by elevated hs-CRP levels with type 2 diabetes mellitus. It was also concluded that advanced age, obesity, poor glycaemic control, and dyslipidaemia were the major correlates of higher hs-CRP levels. To help the type 2 diabetic patients from the very beginning in respect of the prognostic view of macrovascular risk, estimation of serum hs-CRP in the early stage may be a positive enthusiastic intervention. Further studies are required to evaluate hs-CRP as a predictor of deranged cardiovascular risk factors and to explore the influence of modulators including genetic variation on its elevation.

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ORIGINAL ARTICLE

JIACM 2015; 16(1): 16-9

Comparative efficacy and safety of glitazones and DPP-4 inhibitors in type 2 diabetic subjects as add on therapy who had inadequate glycaemic control with prior combination therapy (glimepiride + metformin)

Shalini Gupta, Taruna Sharma**, DC Dhasmana***, Meenakshi Dhar****, Manisha Bisht******

Abstract

***Objectives:** To compare the efficacy and safety of glitazones and DPP-4 inhibitors in type 2 diabetes mellitus as add on therapy, in those patients who had inadequate glycaemic control with prior combination therapy (glimepiride + metformin).*

***Methods:** Thirty patients (previously known cases of type 2 DM), aged above 18 years, attending medicine OPD of Himalayan Institute of Medical Sciences, Dehradun, over a period of one year were included in the study. The eligible patients (N = 30) based on inclusion and exclusion criteria were divided in two groups of 15 patients in each group: Group A, glimepiride + metformin + pioglitazone (G + M + P) and Group B, glimepiride + metformin + sitagliptin (G + M + S). The patients were randomly selected, and the study drugs were given on the basis of physician's discretion and the doses of study drugs were fixed according to their clinical presentation at the time of the inclusion in the study. Patients were then followed-up for a period of 3 months.*

***Results:** The fasting blood sugar level in group A, at day 90 was 147.60 ± 6.06 and in group B was 139.20 ± 3.45 as compared to day 0 (in group A, 185.00 ± 7.59 and in group B was 172.93 ± 8.37).The post-prandial blood sugar level in group A, at day 90 was 206.53 ± 4.27 and in group B was 216.27± 6.80 as compared to day 0 (in group A, 256.07 ± 8.61 and in group B s 271.33 ± 11.98). There was significant ($p < 0.001$) improvement in blood sugar levels (both fasting and post-prandial), in both the study groups but there was no significant inter-group difference among both the study groups.*

***Conclusion:** Glycaemic control in patients included in both groups was significantly better on day 90 as compared to day 0. There was no significant difference in the efficacy and safety of the two combination groups, but there was a marked difference in the cost associated with them.*

***Keywords:** Type 2 diabetes mellitus, pioglitazone, sitagliptin.*

Introduction

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the same phenotype of hyperglycaemia[1], and is caused by a complex interaction of genetics, envoirmental factors and lifestyle choices. Depending upon the aetiology of DM, factors contributing to hyperglycaemia may include reduced insulin secretion, decreased glucose utilisation, and/or increased glucose production[2]. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organs that impose a tremendous burden on the individual with diabetes and on the health care system[3]. DM is known not only for raised blood sugar level but more so for its debilitating and life threatening complications[4]. An estimated 150 million people worldwide have diabetes at present and 300 million are expected to have diabetes by the year 2025[5]. Type 2 DM accounts for ≥ 90% of all diabetic cases. India is being called the diabetic capital of the world[6].

The newly diagnosed subjects are first treated with single antidiabetic agents with other interventions like diet management and physical exercise[7]. Depending on their blood glucose level, drugs are added or changed. The combination therapy is given when the monotherapy is not sufficient to achieve the desired blood glucose level[8]. The inadequate blood sugar control may be because of inadequate drug doses, lack of awareness or poor patient's compliance to the drug. The usual combination in use to treat the type 2 DM is sulfonylureas and biguanides[9]. This combination is effective to correct both fasting and post-prandial hyperglycaemia[10]. In our study, those patients are selected who had inadequate blood sugar control by using the combination of glimepiride and metformin, because of any above said factor. In this study, we used Tzds and DPP-4 inhibitors as add-on therapy in combination with metformin and glimepiride. The aim was to observe the extent of glycaemic control and the safety profile of the study drugs.

Materials and methods

The study was carried out in the Departments of

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Pharmacology and General Medicine, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun, over period of twelve months. Subjects were recruited from among patients attending the Medicine OPD (January to December, 2011).

Type of study: Interventional study.

Sample size: 30 patients were included in the study, were divided into two groups, each group having 15 patients.

Selection of subjects

Inclusion criteria:

1. Patients of either sex and age ≥ 30 years.
2. HbA1c ≥ 8%.
3. Established diagnosis of uncontrolled type 2 DM, without complications.
4. No concurrent illness.
5. Body mass index of 25 - 45 kg/m^2.

Exclusion criteria:

1. Patients of Type 1 DM.
2. Age ≥ 65 years.
3. Presence of any acute or long-term clinically detectable complication.
4. History of acute or chronic kidney disease.
5. History of cardiovascular disease, congestive heart failure, or oedema.
6. Pregnant or lactating women.

Study groups

Patients included in the study were divided into two groups, 15 patients in each group.

Group A: (G + M + P) - glimepiride + metformin + pioglitazone (Tzds).

Group B: (G + M + S) - glimepiride + metformin + sitagliptin (DPP-4 inhibitor).

The drugs were given to patients on the basis of physician's discretion. The dose ranges of drugs were glimepiride 1 - 3 mg/day, metformin 1 - 2 gm/day, pioglitazone 30 mg/day, and sitagliptin 100 mg/day.

Follow-up: Study subjects were followed-up every 15 days for a period of three months. Fasting and post-prandial blood sugar levels were done on each follow-up visit.

Statistical analysis

Interpretation and analysis of obtained results from compared groups were carried-out by using unpaired 't' test for significance and adverse events by using descriptive method.

Results

The fasting blood sugar at the day 90 (i.e., at the end of the three months) in group A was 147.60 ± 6.06 and in group B was 139.20 ± 3.45. There was significant fall in fasting blood sugar level (at the day 90) in all the study drug groups as compared to the fasting blood sugar at day 0 (Table I).

The post-prandial blood sugar at the day 90 (i.e., at the end of three months) in group A was 206.53 ± 4.27 and in group B was 216.27 ± 6.8. Thus there was a significant fall in post-prandial blood sugar level (at the day 90) in all study groups as compared to the post-prandial blood sugar at day 0. The overall difference between the blood sugar (both fasting and post-prandial) values at the day 0 and day 90 in intra-group were highly significant ($p < 0.001$) (Fig. 1). There was no significant inter-group difference between any of the study drug groups as regarding the blood sugar control (Fig. 2).

Table I: Progressive blood sugar control (mg/dl) with the study drug groups in the study period (3 months).

(All values are expressed in mean ± SEM)

n = 30		Group A* (n = 15)	Group B**(n = 15)
Day 0	F	185.00 ± 7.59	172.93 ± 8.375
	PP	256.07 ± 8.61	271.33 ± 11.98
Day 15	F	173.60 ± 7.91	159.33 ± 4.99
	PP	242.80 ± 8.10	244.33 ± 10.00
Day 30	F	167.20 ± 7.07	152.80 ± 4.86
	PP	235.87 ± 7.05	236.80 ± 8.97
Day 45	F	159.07 ± 8.36	148.87 ± 5.28
	PP	226.27 ± 7.02	226.33 ± 7.38
Day 60	F	158.40 ± 8.78	144.00 ± 4.82
	PP	221.47 ± 6.35	216.20 ± 6.85
Day 75	F	157.87 ± 8.01	141.20 ± 4.14
	PP	216.13 ± 4.96	213.60 ± 6.20
Day 90	F	147.60 ± 6.06	139.20 ± 3.45
	PP	206.53 ± 4.27	216.27 ± 6.80

**Group A = G + M + P, **Group B = G + M + S.*

G - glimepiride, M - metformin, P - pioglitazone, S - sitagliptin.

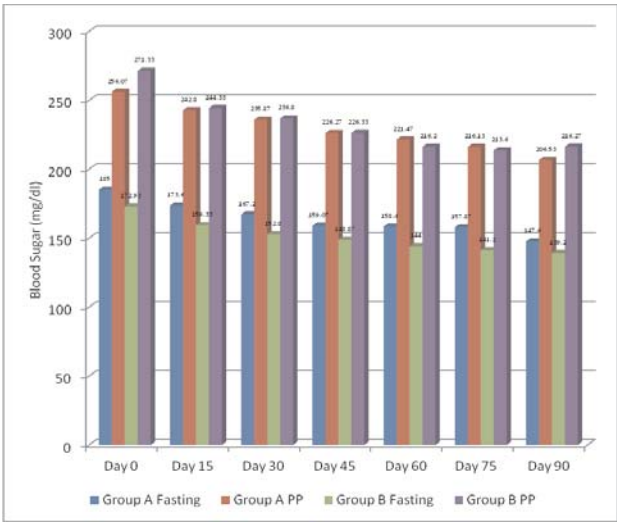

Fig. 1: *Progressive blood sugar control (mg/dl) with the study drug group A and group B in the study period (3 months).*

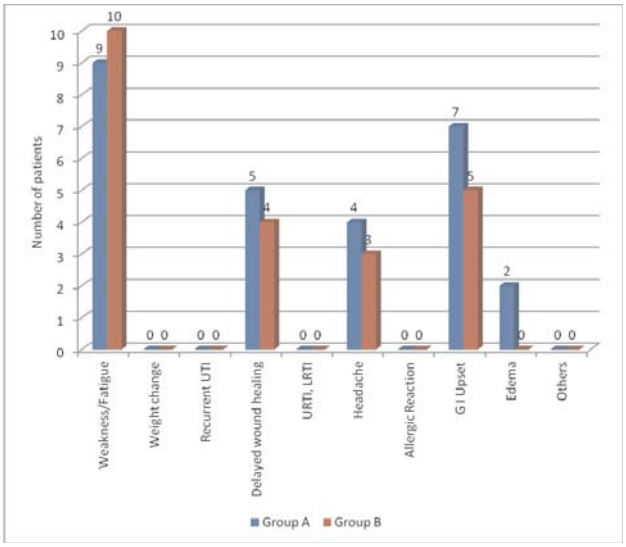

Fig. 2: *Incidence of adverse drug events with the study drug groups over the study period (3 months).*

Discussion

The major classes of oral antihyperglycaemic agents include sulfonylureas, rapid-acting secretagogues, biguanides, alpha-glucosidase inhibitors, thiazolidinediones or DPP-4 inhibitors. These classes are heterogenous in their mode of action and thus have distinct metabolic effect[11]. Commonly used anti-hyperglycaemic agents apart from controlling blood glucose level, provide some other good effects like improvement in lipid profile and decreased level of inflammatory markers, that are related to further disease progression[12,13]. The rationale of add-on therapy in the present study was based on inadequate glycaemic control with the prior drug combination (G + M) in maximum tolerated doses. The doses of the studied drugs were fixed throughout the study period after the selection of patients as per their clinical presentation at the time of the start of study. In an earlier study done to evaluate the efficacy and safety of DPP-4 inhibitors (sitagliptin) in combination with metformin in type 2 diabetic patients, the combination provides substantial and additive glycaemic improvement and was well tolerated in patients who had inadequate glycaemic control with G + M[14,15]. This finding was also substantiated in the present study with significant improvement in the blood glucose level (both fasting and post-prandial) in the group B (G + M + S). The reduction in blood glucose level was seen at the end of day 15 (first follow-up visit) and it was significant. In another study, the effects of Tzds (pioglitazone) on glycaemic control in type 2 diabetic subjects as monotherapy had shown the drugs were highly effective in the treatment of diabetes[16]. These findings have a positive impact on our study as they improve the blood glucose level showing their efficacy towards optimal glycaemic control. In the present study, there was a slightly more reduction in blood glucose level in group-B as compared to group-A suggesting a possible advantage of DPP-4 inhibitors over Tzds, but it is not statistically significant. With these finding we can say that both the studied drugs are quite efficacious in improving the blood glucose level. The trial design, the eligibility criteria, the definition of the end-point and the duration of the study are the factors that may contribute to the difference between our findings and those of other studies. There was no inter-group difference in reduction from baseline in both fasting and post-prandial blood glucose level. Our study did not find any serious side effect associated with either study drug groups. Weakness and fatigue were the most common adverse effects and were seen most frequently in both groups, but this can also be explained by the fact that weakness and fatigue are most common presenting features of the type 2 DM, especially in those subjects with blood glucose level beyond the normal limits[17]. To conclude, add-on therapy was seen to be effective in lowering the blood glucose level (both fasting and post-prandial) when used in combination with the other OHAs (G and M). In view of the positive effects seen in all parameters with the use of combination therapy, it can be assumed that if the therapy had been continued for a longer duration, even better results would be seen. In the present study, the sample size and the duration of study might not be sufficient enough to demonstrate inter-group difference in efficacy and their effect on other parameters. Hence, keeping these limitations in view, caution is to be exercised while interpreting the results of this study.

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"Luck is what happens when preparation meets opportunity."

– ELMER LETTERMAN.

ORIGINAL ARTICLE

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Changing clinical profile of dengue fever in Delhi in 2011

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Abstract

Aim: To study the clinical and laboratory profile of dengue fever, dengue haemorrhagic fever, and dengue haemorrhagic shock syndrome from August-September 2011 in a Delhi hospital.

Method: An observational study of 58 cases was done noting the clinical and laboratory profile of dengue fever, dengue haemorrhagic fever, and dengue haemorrhagic shock syndrome cases admitted in a Delhi hospital and diagnosed as per WHO 1997 scheme. Routine laboratory investigations and special investigations as and when needed were done with exclusion of malaria. Dengue serology by capture Elisa for IgM for dengue virus was done in all cases. Data was analysed by Microsoft excelepi-info software for means and proportions. Note was made of atypical cases and their presentation.

Results: Amongst 58 cases, the mean age was 31.8 years with majority 80.7% being males. 53.4% cases tested positive for dengue serology IgM by capture Elisa. Bleeding manifestations were seen only in 32.8% even though platelets were less than 1,00,000/ cumm in 94.8% cases. GIT manifestations such as pain abdomen, vomiting and anorexia was seen in 55.2% cases. Jaundice was seen in 20.7% with high proportion of transaminitis (SGOT 83.9% and SGPT 78.6%). Non oliguric renal azotemia in absence of DSS was seen in 22.4% cases.15.5% cases had atypical manifestations such as myocarditis, acalculous cholecystitis, communicating hydrocephalus, encephalopathy, pulmonary haemorrhage, liver abscess with DVT and septic pulmonary embolism, and subacute intestinal obstruction.

Conclusions: A shift in the clinical profile of dengue fever and DHF has been observed where the incidence of DSS has fallen and organ specific clinical profile has increased with hepatic transaminitis being almost universal along with atypical cases such as encephalopathy, acalculous cholecystitis, renal azotemia, myocarditis, and pulmonary haemorrhage. With IgM positivity rate of 41% - 53.4% half the cases appear to be secondary dengue infection presenting with autoimmune complex type clinical disease.

Introduction

Over the past 15 years, dengue fever (DF)/dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) has been a leading cause of hospitalisation in the WHO South-East Asia region. During the 1996 - 1998 epidemic, high mortality was observed in India, Indonesia, Maldives, Myanmar, and Sri Lanka[1]. All four serotypes (DEN1-4) have been isolated and are in circulation. The clinical spectrum of dengue depends upon the virulence of the serotype/genotype, primary or secondary infection, and immune status of the population[2]. A changing trend of the clinical spectrum has been observed over the last decade wherein the DHF/DSS cases are being seen less frequently and an increasing trend towards atypical manifestations with organ dysfunction is being witnessed in the Asian subcontinent. Various atypical clinical presentations of DF/DHF pose not only diagnostic challenge but also get mismanaged. An observational case series at our tertiary care hospital was undertaken to elucidate the various presentations of DF/DHF.

Methods

This was an observational study (case series) conducted in the department of medicine at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, a tertiary care teaching hospital. We selected the patients admitted with the signs and symptoms suggestive of dengue fever, dengue haemorrhagic fever, and dengue haemorrhagic shock during the months of August and September 2011 as per the WHO scheme (1997)[3] which classifies symptomatic dengue virus infections into three categories; undifferentiated fever, dengue fever, and DHF. Dengue fever was clinically defined as an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, or leucopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. DHF was defined as: fever or history of fever lasting 2 - 7 days; a haemorrhagic tendency shown by a positive tourniquet test or spontaneous bleeding; thrombocytopenia; and evidence of plasma leakage shown either by haemoconcentration with substantial changes in serial measurements of packed-cell volume, or by the development of pleural effusions or ascites, or both. Dengue shock syndrome was defined as DHF with hypotension (DSS III) and shock (DSS IV).

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All the patients selected were evaluated through detailed clinical history taking and physical examination by the physician. Laboratory investigations were also conducted and included complete haemogram with platelet count, blood urea nitrogen and serum creatinine, liver function tests (serum bilirubin, alanine amino transferases, aspartate amino transferases and alkaline phosphatase), serum electrolytes (Na^+, K^+), malaria parasite antigen.

Dengue serology for all the patients was performed by the ELISA test to detect IgM antibodies against dengue virus in the patient's sera. Venous blood samples were collected from all the patients under aseptic conditions. All sera were tested for the presence of specific dengue virus IgM antibodies using a chikungunya-IgM antibody capture-ELISA kits provided by Arbovirus Diagnostics, National Institute of Virology, Pune, India. The test is an IgM capture ELISA by using a 96-well microtitre plate coated with anti-human IgM. For quality control, two positive and two negative controls were put up for the validation of the kit supplied. The expected values for the positive and the negative were: Positive - OD values more than or equal to 0.5; and negative - OD values less than or equal to 0.18. Sample tested was considered positive if it exceeded OD value of the negative control by a factor of 4.0 (sample OD $\geq$ negative OD x 4.0)[4]. Chest radiography, abdominal ultrasound, non-contrast computerised tomography (NCCT) of head, two-dimensional echocardiography and other relevant radiological investigations were conducted wherever required. Informed consent was taken from all the patients.

The data was entered in the Microsoft excel sheet and analysed using Epi-info software. Means and proportions were calculated.

Results

A total of 58 patients were admitted during the study period. The mean age (SD) of the patients was 31.8 (14.1) years and majority 46 (80.7%) of the patients were males. All the patients were tested for dengue serology and 31 (53.4%) of the patients had positive dengue serology. Other than fever, the common clinical features were retro-orbital pain 26 (44.8 %) and pain abdomen 25 (43.1%). Bleeding manifestations (epistaxis/haemoptysis/malena/ sub-conjunctival haemorrhages/petechiae) were present in 19 (32.8%) of the patients. More than half (52.6%) of the patients who had bleeding manifestation were positive for dengue serology. GIT manifestations were present in 32 (55.2%) of the patients. Main clinical features among GIT manifestations were pain abdomen 25 (78.1%), vomiting 18 (56.2%), and decreased appetite 13 (40.6%). Signs and symptoms of jaundice were present in 12 (20.7%) of the patients, out of which three had positive dengue serology (Table I).

Table I: Clinical features of patients with dengue fever (DF) and dengue haemorrhagic fever (DHF) admitted in August and September, 2011.

S.No.	Clinical features	Total cases no(%)	Cases with positive dengue serology no (%)
1.	Fever	58(100)	31(100)
2.	Vomiting	18(31.0)	8(25.8)
3.	Pain abdomen	25(43.1)	11(35.5)
4.	Diarrhoea	6(10.3)	1(3.2)
5.	Jaundice	12(20.7)	3(9.7)
6.	Shortness of breath	6(10.3)	1(3.2)
7.	Decreased appetite	15(25.9)	8(25.8)
8.	Retro-orbital pain	26(44.8)	17(54.8)
9.	Rash	11(19.0)	6(19.4)
10.	Epistaxis	5(8.6)	4(12.9)
11.	Haemoptysis	5(8.6)	3(9.7)
12.	Malena	9(15.5)	3(9.7)
13.	Abdominal distension	9(15.5)	4(12.9)
14.	Altered sensorium	4(6.9)	1(3.2)
15.	Petechiae	7(12.1)	3(9.7)
16.	Subconjunctival haemorrhage	4(6.9)	2(6.5)
17.	Ascites	6(10.3)	1(3.2)
18.	Pleural effusion	5(8.6)	Nil
19.	Pedal oedema	3(5.2)	Nil
20.	Hepatomegaly	3(5.2)	Nil
21.	Splenomegaly	Nil	Nil
22.	Mean no. of days of hospital stay (SD)	4.8(2.2)	4.6(2.1)

Most of the patients 55 (94.6%) had platelet count less than 1,00,000/mm^3 and half of the patients had platelet count less than 20,000/mm^3. Packed cell volume was more than 36.3% in 23 (41.1%) of the patients. Leucopoenia (TLC < 4,000/mm^3) was present in 14 (24.1%) of the patients. The liver function tests revealed raised SGOT and SGPT in 47 (83.9%) and 44 (78.6%) of the patients respectively. Renal functions (serum creatinine > 1.3 mg/ dl and/or serum urea > 40 mg/dl) were deranged in 13 (22.4%) of the patients. No significant difference was found in the mean levels of platelet count, PCV, SGOT and SGPT between the patients with the positive and the negative

dengue serology. All the patients were negative for malaria parasite antigen (Table II and III).

Table II: Laboratory investigations of patients with dengue fever (DF) and dengue haemorrhagic fever (DHF) admitted in August and September, 2011.

SNo	Lab. parameters (units)	All patients with signs and symptoms of DF/DHF N = 58 mean (SD)	Patients with sign and symptoms of DF/DHF with positive dengue serology N = 31 mean (SD)
1.	Haemoglobin (gm/dl)	11.8 (3.1)	12.8 (2.6)
2.	Total leucocyte count per mm^3	6,505 (3598)	6,677 (3755)
3.	Packed cell volume (%)	36.3 (8.6)	38.6 (7.4)
4.	Blood urea nitrogen (mg/dl)	32.5 (25.0)	29.0 (21.0)
5.	Serum creatinine (mg/dl)	0.8 (0.3)	0.8 (0.3)
6.	Serum bilirubin (mg/dl)	1.0 (1.9)	0.6 (0.4)
7.	SGOT (IU/l)	134.7 (120.2)	152.2 (136.6)
8.	SGPT (IU/l)	88.8 (66.1)	97.3 (70.6)
9.	Alkaline phosphatase (IU/l)	265.1 (127.2)	249.9 (116.8)
10.	Sodium (meq/l)	135.7 (5.1)	135.5 (5.9)
11.	Potassium (meq/l)	4.1 (0.7)	4.1 (0.7)

Table III: Platelet count (per mm^3) N = 58.

Range	Numbers (%)
Less than or equal to 20,000	28 (48.3)
21,000 to 40,000	14 (24.1)
41,000 to 60,000	8 (13.7)
61,000 to 80,000	3 (5.2)
81,000 to 1,00,000	2 (3.4)
More than 1,00,000	3 (5.2)

Patients of dengue presenting with atypical clinical features

Total 9 (15.5%) patients admitted with dengue fever had other atypical presentations (Table IV). Four patients had CNS manifestations. A 70-years-old male who presented with fever and drowsiness was diagnosed with communicating hydrocephalus (Fig. 1), 2 males who presented with fever and altered sensorium were diagnosed with encephalopathy, and a 55-years-old female who presented with fever and altered sensorium was diagnosed with subacute cerebral infarct of left parietal region. Two patients had myocarditis, both were young males and had generalised hypokinesia with reduced LV systolic function on 2D echo which recovered within 7 - 10 days. One 50-years-old female who presented with fever, vomiting, pain abdomen, loose motions, malena, and breathlessness, had pulmonary haemorrhage resembling pneumonia (Fig. 2a and 2b). Two patients had acalculus cholecystitis out of which one had a liver abscess (Fig. 3a) with left lower limb DVT with septic pulmonary emboli in left lower lobe (Fig. 3b), with right mid-zone partial collapse with bilateral pleural effusion. One patient, a 29-years-old male with fever, vomiting, loose motions with icterus with haemoptysis, malena was diagnosed with self-limiting subacute intestinal obstruction with minimal ascites.

Discussion

53.4% cases in our study were IgM positive by ELISA capture which is similar to percentage of seropositivity (41%) in DHF cases from Chennai in 2007 series. This could be probably because half the cases may be secondary cases wherein the reported seropositivity for IgM which peaks around 2 weeks post-infection is around 30%[5]. The occurrence of retrobulbar pain (44.8%) and abdominal pain (43.1%) was similar to case series from Kerala in 2003[2]. Bleeding manifestations were higher in our cases (32.1%) compared to cases in the Kerala series, but similar to incidence in paediatric cases (38.8%) from the Lucknow series in 2008[6].

In our series, only 18.9% cases had capillary leak manifestations of pleural effusion and ascites which is case-defining as per the WHO case definition. Only 33.6% DHF/DSS cases were found in case series from Kerala in 2003[2]. No case of shock was seen in our series as compared to 23.5% cases in the 1996 Delhi outbreak[7].

The liver enzymes were raised in a large number of cases with SGOT (83.9%) and SGPT (78.6%). SGOT values higher than SGPT were similar to the liver enzyme pattern in the kerala series (84%)[2] and also in Delhi epidemic of 1996 (90%)[7]. The higher SGOT than SGPT has been attributed to ischaemic hepatitis on account of hypotension associated with DHF in the Chennai series[8]; but in our series, liver enzymes were elevated (SGOT > SGPT) in absence of any hypotension. The elevation of liver enzymes was associated with worst outcome in cases from the Kerala series[2] but no such association was noticed in our series. The incidence of hepatomegaly varies from 5.2% to 17.2% in various series of adult cases[2,7,8] including ours. Jaundice varies from 1% - 20.7% in adults. On the contrary, a much higher incidence of hepatomegaly (62.5%) and splenomegaly (60%) has been reported in children from North India[7] for which no definite explaination exists. Though not tabulated, we have

observed splenomegaly in cases with mixed infections with malaria. No case of splenomegaly was seen in our series since we excluded cases with mixed infection.

Atypical cases of dengue fever with acute abdomen have been reported. Acalculous cholecystitis manifesting as acute abdomen was noted in two cases in our series. This

Table IV: Atypical clinical presentation of dengue fever cases.

SNo	Atypical clinical presentation	No. of patients	Patient profile and clinical features	Lab. parameters
1.	Myocarditis	Two	27-years male fever 7 days	Platelets count: 80,000/mm^3 2D echo: Generalised hypokinesia with dilated chambers with LVEF = 30%, with mild TR with moderate MR, normal study after one week CECT thorax: Mild cardiomegaly with bilateral pleural effusion
			26-years male, fever with chills 10 days with body aches	Platelet count: 64,000/ mm^3 2D echo: mild left ventricular systolic dysfunction with global hypokinesia (LVEF 40%)
2.	Communicating hydrocephalus	One	70-years male, fever 4 days with retro orbital pain and altered sensorium	Platelet count: 17,000/mm^3 CXR: left pleural effusion NCCT head: communicating hydrocephalus
3.	Encephalopathy	One	65-years male, fever 10 days with altered sensorium with bilateral plantar withdrawal Pupils: Non-reactive	Hb: 8.3 gm/dl TLC: 1,800/mm^3 Platelet count: 20,000/mm^3 Alkaline phosphatase: 245 IU
4.	Cerebral infarct	One	55-years female, fever 7 days with altered sensorium	Platelet count: 1,42,000/ mm^3, blood urea: 23 mg/dl Serum creatinine: 1.6 mg/dl NCCT: Subacute infarct at left parietal region Dengue serology: positive
5.	Pulmonary haemorrhage	One	50-years female, fever 4 days with vomiting, pain abdomen, loose motions, shortness of breath, and malena	Haemoglobin: 9.1 gm/dl, TLC: 2,100/mm^3, Platelet count: 29,000/mm^3, CXR: Inhomogenous opacity in right middle and lower zone CECT chest: ground glass opacity rt middle and lower lobe and left lower lobe suggestive of alveolar haemorrhage.
6.	Acalculus cholecystitis	One	35-years male, fever 7 days and pain abdomen and retro-orbital pain	Platelet count: 21,000/mm^3, PCV: 45.9%, SGOT: 189 IU, SGPT: 200 IU, Alkaline Phosphatase: 421 USG abdomen: Mild ascitis with thick gall bladder
7.	Acalculus cholecystitis with DVT left lower limb with left lower lobe septic pulmonary emboli with bilateral pleural effusion with liver abscess	One	45-years male, fever 9 days, pain and swelling left lower limbs for 4 days Pallor present Chest: right lower zone inspiratory crepts	Hb: 8 gm/dl, platelets count: 16,000/ mm^3 Alkaline phosphatase: 421 IU, PT/INR: 15s/1.12 aPTT: 30.2, FDP: 20 CXR: Right mid-zone patchy opacity with bilateral pleural effusion Venous doppler lower limbs: DVT (left lower limb) HRCT thorax: Right lower lobe septic emboli in superior segment of lung with right mid-zone partial collapse with bilateral pleural effusion USG abdomen: Hepatomegaly with well demarcated mixed hypoechoic lesion in left lobe of liver with thickened and oedematous gall bladder with minimal pericholecystic fluid collection
8.	Sub-acute intestinal obstruction (SAIO)	One	29-years male with fever, vomiting, loose motions with icterus with haemoptysis, malena	Haemoglobin: 4.7 gm/dl, TLC: 3,100/mm^3 Blood urea: 79 mg/dl, serum bilirubin: 6.0 mg/dl SGOT: 456 IU, SGPT: 273 IU Alkaline phosphatase: 299 IU, PT: 22 s, USG abdomen: Subacute intestinal obstruction with minimal ascites

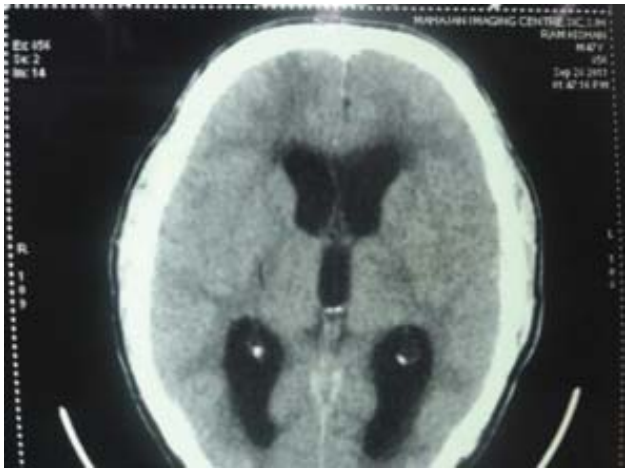

Fig. 1: *NCCT head showing communicating hydrocephalus.*

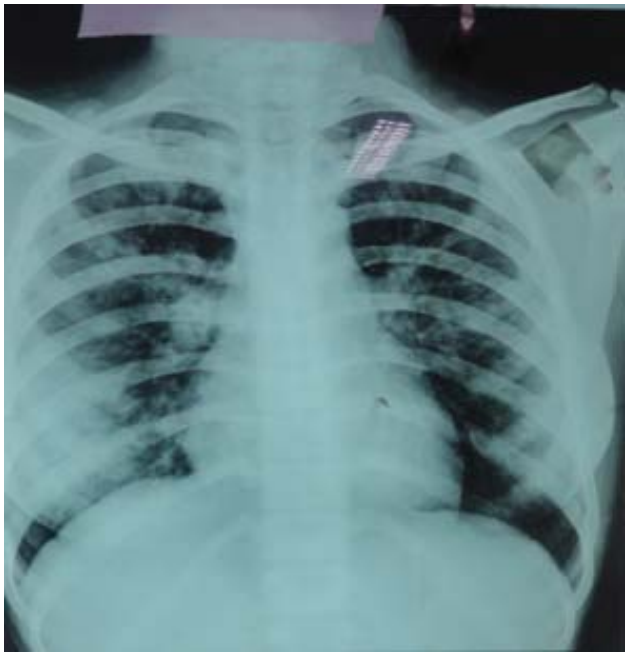

Fig. 2a: *X-ray chest showing inhomogenous opacity in right middle and lower zone.*

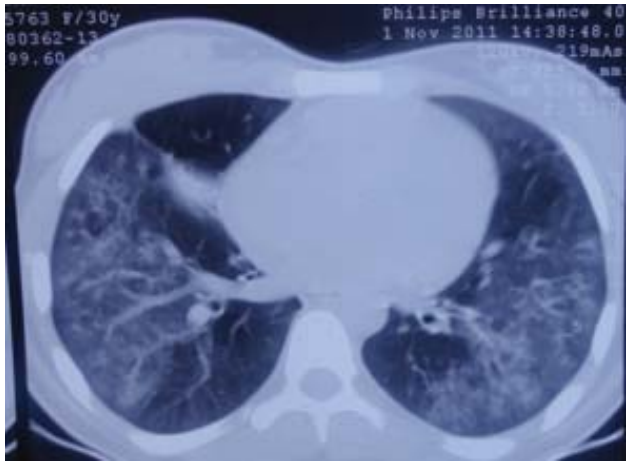

Fig. 2b: *CECT chest showing ground glass opacity right middle and lower lobe and left lower lobe suggestive of alveolar haemorrhage.*

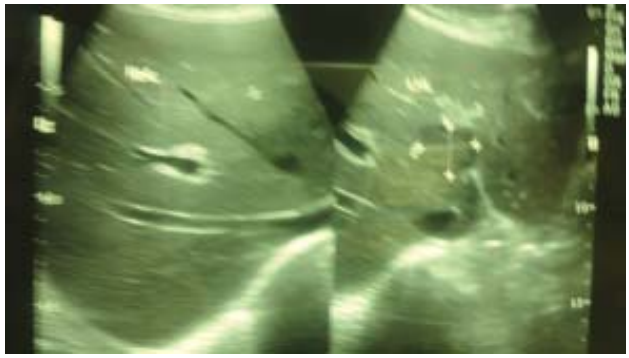

Fig. 3a: *USG abdomen showing left lobe liver abscess.*

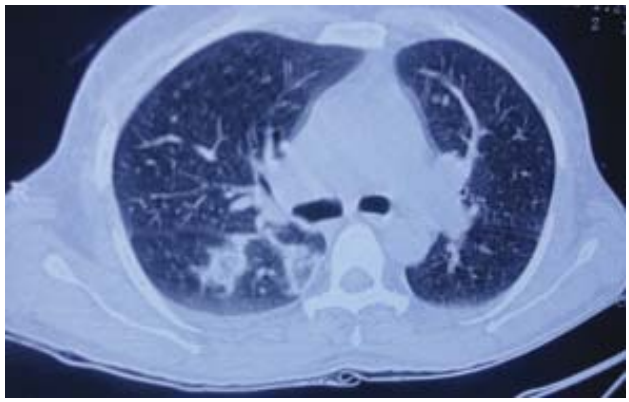

Fig. 3b: *HRCT thorax showing right lower lobe septic emboli in superior segment of lung with right mid-zone partial collapse.*

is mainly attributed to increased vascular permeability leading to gallbladder wall oedema and thickening which is usually self-limiting. One case was found to have liver abscess in addition to acalculous cholecystitis along with deep vein thrombosis of the calf veins and septic pulmonary embolism, bilateral pleural effusion with severe thrombocytopenia (16,000/cumm) in the absence of DIC not reported in the literature earlier. The case had complete recovery with standard treatment. Though not seen in our series, rarely acute pancreatitis has also been reported[9]. Another case of self-limiting sub-acute intestinal obstruction without electrolyte imbalance but dengue hepatitis not reported in literature was seen which probably could be due to bowel wall oedema.

Elevated renal parameters have been reported in adults from Chennai[8] with DHF in direct proportion to severity of DHF with hypotension and in 30.7% cases with shock and only 6.5% without shock in seropositive children[10]. We observed non-oliguric renal azotemia in 22.4% cases

in our series without any hypotension.

Encephalopathy in dengue is believed to be due to cerebral oedema, hyponatraemia, hypoperfusion, or intracranial bleed[11], and also active dengue virus invasion of the brain[12]. Acute demyelinating encephalomyelitis and hepatic dysfunction has also been reported to be a cause[13]. We observed altered sensorium in 6.9% cases. Impaired consciousness was seen in 5% cases in the 1996 Delhi epidemic of dengue[8] whereas high proportion (53.7%) was seen in children with dengue from Lucknow in 2008[6]. We observed a self-limiting atypical case of communicating hydrocephalus as a cause of altered sensorium which was possibly due to extreme degree of interstitial cerebral oedema not reported earlier in the literature. The CSF study was not attempted but MRI brain did not reveal any structural changes in brain. In another atypical case with IgM sero-positivity, a posterior parietal cerebral infarct leading to altered sensorium and behaviour without any electrolyte imbalance or haemorrhage in the infarct was seen. This could probably be due to dengue autoimmunity resulting in vasculitis.

We observed shortness of breath in 10.3% cases. Increased permeability of alveolar capillary membrane resulting in oedema of alveoli and interstitium leads to pulmonary dysfunction. ARDS has been reported in DSS[14] and DHF[15,16]. Early restoration of adequate tissue perfusion with due care to avoid excessive fluid overload in order to prevent progression to ARDS is a clinically challenging situation in such cases. One case of pulmonary haemorrhage mimicking pneumonia with shortness of breath was seen in our series. Pulmonary haemorrhage has been reported in DHF with ARDS[16,17].

2 cases of self-limiting myocarditis with LV systolic dysfunction were seen in our series with sinus tachycardia in the absence of any shortness of breath or associated arrhythmias. Literature shows asymptomatic cases of self-limiting myocarditis with cardiac rhythm disorders such as atrial fibrillation, sinus node dysfunction, or ventricular ectopics with and without echocardiographic findings[18,19,20]. The myocarditis is mostly seen to recover in 7 - 10 days after onset of fever. Direct infection of cardiomyocytes with dengue virus in children with DHF has also been reported with derangement of myotubular Ca^{2+} storage as a contributor to myocarditis[21].

Large percentage of dengue DF/DHF cases presented with transaminitis which along with WHO criteria for case definition of dengue[3] appears to be a differentiating feature of dengue as also noted by Chandrakanta *et al* in north Indian children with dengue fever in 2008. Over the years, increasing incidence of transaminitis and also non-oliguric renal dysfunction with decreasing incidence of DSS as observed in our series could possibly be explained by organ specific autoimmunity triggered by a Th1 to Th2 shift in the immune cascade as well as role of Th17 cells which are potent inducers of autoimmunity[22] in a community where most are of secondary infection due to previous dengue virus infection presenting with clinical picture of immune complex type disease.

Conclusion

A shift in the clinical profile of dengue fever and DHF has been observed over the last decade in India where the incidence of DSS has been falling and organ specific clinical profile is increasing with hepatic transaminitis being almost universal along with atypical cases such as encephalopathy, acalculous cholecystitis, renal azotemia, myocarditis, and pulmonary involvement being seen in most series. With IgM positivity rate of 41% - 53.4%, half the cases appear to be secondary dengue infection presenting with autoimmune complex type clinical disease.

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Rozavel F

ORIGINAL ARTICLE

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Comparative evaluation of IADPSG criteria with ADA and WHO criteria for diagnosis of gestational diabetes mellitus

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Abstract

***Objective:** To evaluate American Diabetes Association (ADA), World Health Organization (WHO) and International Association of Diabetes and Pregnancy Study Group (IADPSG) diagnostic criteria for gestational diabetes mellitus (GDM) against pregnancy outcomes and complications.*

***Materials and methods:** This study enrolled women, with their estimated gestational age between 24th and 28th weeks, attending ANC clinic at PGIMS, Rohtak. After informing, women who consented to participate were given a standardised 2 h 75 g oral glucose tolerance test (OGTT). History of urinary tract infection, pre-eclampsia, mode of delivery and birth weight of newborn were recorded and analysed.*

***Results:** A total of 607 women participated in the study. Out of these, 43 (7.1%) were diagnosed as GDM by ADA criteria, 116 (19.11%) by WHO criteria and 144 (23.72%) by IADPSG criteria. No statistically significant difference was observed between GDM and normal women in case of urinary tract infection, though it occurred more frequently in GDM (defined by any of three criteria) women. Pre-eclampsia was significantly more common in women with GDM defined by ADA criteria. Caesarean delivery was more frequent in GDM women defined by ADA and WHO criteria, but no significant difference was seen. Caesarean delivery was observed 1.4 times more frequently in normal women compared to GDM women (defined by IADPSG criteria) though no significant difference was observed between the two groups. Mean birth weight of newborn was also not significantly different between GDM (defined by any of three criteria) and normal women.*

***Conclusion:** Though both WHO and IADPSG criteria detected more cases of GDM, both of these criteria failed to predict adverse pregnancy outcomes. The recent IADPSG criteria need to be validated in various population groups before they can be universally accepted for diagnosing and treating GDM.*

***Keywords:** GDM, diagnostic criteria, comparison.*

Introduction

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy[1,2]. The prevalence of GDM varies from 3.8% to 21% in various parts of India, as reported in different studies[3,4]. This wide difference in prevalence of GDM as reported in these studies may be because of different criteria used for diagnosing GDM as well as the heterogeneity of Indian population with different regional customs, religions, and dietary habits.

Earlier, the American Diabetes Association (ADA) recommended using 100 g 3 hr oral glucose tolerance test (OGTT) for diagnosing GDM[2]. Though the 100 g 3 hr OGTT is still recommended by ADA, it has also included use of 75 g 2 hr OGTT in diagnosing GDM[2]. World Health Organization (WHO) recommends the use of 2 hr 75 g OGTT for diagnosing GDM[5]. The fasting value suggested by the WHO panel is similar to that diagnostic of DM in non-pregnant individuals and the 2 hr value is similar to that diagnostic of impaired glucose tolerance in non-pregnant individuals[5].

The most recent guidelines are by the International Association of Diabetes and Pregnancy Study Group (IADPSG)[6]. These guidelines are based on a stepwise consideration of HAPO study data leading to recommendations of values for fasting, 1 hour, and 2 hour plasma glucose concentration as diagnostic thresholds. These thresholds were the average glucose values at which odds for birth weight > 90th percentile, cord blood C-peptide > 90th percentile, and per cent body fat > 90th percentile reached 1.75 times the estimated odds of these outcomes at mean glucose values. At least one of these thresholds must be equaled or exceeded to make a diagnosis of GDM.

The ADA and WHO criteria have been studied for predicting adverse pregnancy outcomes and have been found to be effective in predicting adverse outcomes[7]. The IADPSG recommendations have been studied little in terms of predictive ability for adverse pregnancy outcomes. Thus, the objective of this study was to evaluate ADA, WHO and IADPSG diagnostic criteria for GDM against pregnancy outcomes and complications

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which are urinary tract infections, pre-eclampsia, caesarean delivery, and mean birth weight of newborn.

Materials and methods

This study was conducted in the antenatal care clinic at Post-Graduate Institute of Medical Sciences, Rohtak, Haryana. In an earlier study done at various centres across India, the prevalence of gestational diabetes mellitus was found to be 16.55%[4]. Assuming the prevalence as 16.55%, and allowable errors of 20% at level of significance of 95%, a sample of 500 eligible subjects was calculated. The study protocol was approved by the local institutional ethics committee. All women were informed about the nature of the study and those who consented were included in the study. All pregnant women with estimated gestational age between 24th and 28th weeks were included in the study. Women who were known diabetics, or who were suffering from any chronic renal, pancreatic, or other severe illness were excluded from the study. A pro forma containing general information on demographic characteristics, socio-economic status, parity, family history of diabetes and/or hypertension and past history of GDM was filled up. The subjects were advised to observe overnight fast (at least 8 hrs but not more than 14 hrs.) and were called at PGIMS, Rohtak in the morning for 75 gm OGTT. The venous blood sample was taken in fasting state, 1 and 2 hours after consuming 75 gm anhydrous glucose. The plasma glucose was estimated by GOD-POD method by using Siemens kit. While waiting after the intake of 75 g glucose, the subjects were asked to avoid physical activity during the next 2 hrs. Anthropometry (weight, height, BP, etc.) was done after OGTT. All the women participating in the study were followed throughout their gestation and details regarding urinary tract infection (UTI), pre-eclampsia, mode of delivery, and birth weight of the newborn were collected.

According to diagnostic criteria recommended by ADA for a 2 hr 75 g OGTT, GDM is diagnosed if two or more plasma glucose levels meet or exceed the following thresholds, fasting glucose concentration of 95 mg/dl, 1 hour glucose concentration of 180 mg/dl, and 2 hour glucose concentration of 155 mg/dl[2]. Defined by WHO criteria, GDM is diagnosed with a threshold plasma glucose concentration greater than or equal to 140 mg/dl (7.8 mmol/l) at 2 hours similar to that of impaired glucose tolerance test (IGT) in non-pregnant or fasting plasma glucose concentration greater than or equal to 126 mg/dl (7.0 mmol/l)[5]. IADPSG criteria require a fasting plasma glucose > 92 mg/dl, a 1 hour post-load plasma glucose $\geq$ 180 mg/dl or a 2 hour post-load plasma glucose $\geq$ 153 mg/dl for diagnosis of GDM using a 75 g OGTT[6].

BMI was calculated based on reported pre-pregnancy weight of participant. Urinary tract infection was defined as a symptomatic condition and for which the participants took treatment from their obstetrician. Pre-eclampsia was defined as a history of hypertension after 20th week gestation with pedal oedema for which urgent treatment was started or history of hypertension for which patient was admitted and early delivery was contemplated. Women with history of caesarean delivery in previous pregnancy were not included for delivery outcome. All women diagnosed having GDM were given medical nutrition therapy (MNT) by a trained dietician. Insulin therapy is given when nutrition therapy fails to maintain self-monitored glucose at $\leq$ 105 mg/dl, $\leq$ 155 mg/dl and $\leq$ 130 mg/dl at fasting, 1 and 2 hours respectively.

Statistical analysis: According to the objectives of the study, the collected data was compiled, tabulated, and analysed using appropriate statistical tests. The chi-square test and Fisher's exact test (two-sided) were carried-out to test the difference between two proportions. T-test was performed to test the difference between two means. All statistical analyses were performed using SPSS version 17.0 software.

Results

615 women were screened for this study. Out of these, five women were found to have their plasma glucose in diabetic range and were started on insulin treatment. Three women required addition of insulin therapy as MNT failed to bring their plasma glucose to the target range. The remaining 607 women were enrolled in the present study and their baseline characteristics are shown in Table I. GDM was diagnosed in 43 (7.1%) women based on ADA criteria. Out of these 43, 17 women had all 3 values abnormal on OGTT and 26 women had 2 abnormal values. A single abnormal value was observed in 66 (10.87%) women, in whom fasting plasma glucose was the most common abnormal value seen in 55 women. 116 (19.11%) women were diagnosed as GDM using the WHO criteria. WHO criteria detected 74 additional women with GDM while it missed one GDM woman detected by ADA criteria. By using the latest IADPSG criteria, 144 (23.72%) women were diagnosed as GDM. This criterion detected all the GDM women as diagnosed by ADA criteria and an additional 101 (16.6%) women as having GDM. IADPSG criteria missed 49 GDM women as detected by WHO criteria. 18 women had all the three values abnormal on 2 hr OGTT while 26 women had two abnormal values. A single abnormal value was seen in 100 women, out of whom, 87 had an abnormal fasting value of plasma glucose, 9 had an abnormal 1 hr value, and 4 had an abnormal 2 hr value on OGTT.

Table I: Showing the baseline characteristics of the study population.

Age (years)	
16 - 20	110 (18.1)
21 - 25	353 (58.2)
26 - 30	121 (19.9)
> 30	23 (3.8)
BMI (kg/m^2)	
< 18.5	232 (38.2)
18.5 - 24.9	325 (53.6)
> 25	50 (8.2)
Parity	
0	254 (41.8)
1	245 (40.4)
2	73 (12.0)
> 3	35 (5.8)
Education	
Professional/post-graduate/graduate	133 (21.9)
Intermediate/high school/middle school	372 (61.3)
Primary school	72 (11.9)
Illiterate	30 (4.9)

Table II shows frequency of pregnancy outcomes in GDM and normal women categorised according to different criteria. Though UTI during pregnancy was found to be more common in women with GDM (ADA criteria; 16.3% in women with GDM compared to 8.7% in women without GDM), this association did not reach statistical significance (p = 0.097). Also, no significant association was found between GDM (as defined by WHO or IADPSG criteria) and UTI during pregnancy (p = 0.239 and 0.371, respectively).

Pre-eclampsia was seen more frequently in women with GDM (as defined by ADA criteria) compared to women without GDM (11.8% compared to 3.0%), and this association was found to be statistically significant (p = 0.032). Even though pre-eclampsia was encountered more frequently in GDM (defined by WHO and IADPSG criteria) women, no significant difference was observed compared to normal women (p = 0.334 and p = 0.133, respectively).

Caesarean delivery was observed more frequently in GDM women compared to women without GDM (defined by either ADA or WHO criteria). Using ADA criteria, 11.8% of GDM women underwent caesarean delivery compared to 9.7% normal women, but the difference was not statistically significant (p = 0.761). WHO criteria predicted similar outcome with more frequent caesarean delivery in GDM women but no significant difference was observed (p = 0.287). IADPSG criteria predicted a different outcome altogether, i.e., frequency of caesarean delivery was more than 1.4 times as common in normal women compared to women with GDM (10.8% compared to 7.5%), though this was not statistically significant (p = 0.341).

Table II: Frequency of pregnancy outcomes in GDM and normal women categorised according to different criteria.

	Frequency in GDM women	Frequency in normal women	p-value
UTI during pregnancy			
ADA	16.3	8.7	0.097
WHO	12.1	8.6	0.239
IADPSG	11.1	8.6	0.371
Pre-eclampsia			
ADA	11.8	3.0	0.032
WHO	5.8	3.2	0.334
IADPSG	6.5	2.8	0.133
Caesarean delivery			
ADA	11.8	9.7	0.761
WHO	12.9	9.0	0.287
IADPSG	7.5	10.8	0.341

Table III shows mean birth weight of newborn delivered by GDM and normal women. As can be seen, the mean birth weight was almost equal for these two groups defined by ADA criteria (2.774 ± 0.438 kg in GDM women compared to 2.788 ± 0.500 kg in normal women; p = 0.882). Both WHO and IADPSG criteria predicted higher birth weight of newborn in GDM women, but the difference was not statistically significant (p = 0.529 and p = 0.643, respectively).

Table III: Mean birth weight of newborn by different criteria.

	GDM	Normal	p-value
ADA	2.774 ± 0.438	2.788 ± 0.500	0.882
WHO	2.818 ± 0.504	2.778 ± 0.492	0.529
IADPSG	2.807 ± 0.444	2.779 ± 0.512	0.643

Discussion

Prevalence of GDM varies across different regions of India.

It ranges from 3.8% to 21%[3,4]. This difference in prevalence could be partly because of difference in cultural practices and ethnicity in different regions as well as because of difference in criteria and protocols used for diagnosis of GDM. As observed in our study, use of different criteria can lead to a very huge difference in prevalence rates of GDM in a study population. Using the ADA criteria, 7.1% women were found to have GDM, while WHO and IADPSG criteria detected 2.8 and 3.4 times more women as having GDM, respectively. India, being a developing country with the second highest population in the world, cannot afford the burden posed by such a high prevalence of GDM until the data is validated against adverse pregnancy outcomes in the population. Various studies in different regions of the world have shown adverse pregnancy outcomes to be associated with GDM defined by ADA and WHO criteria. IADPSG criteria itself is based on adverse pregnancy outcomes in HAPO study.

In our study, though UTI was observed to occur more frequently in women with GDM, no significant difference in proportions was observed compared to normal women and it can be concluded that UTI is not associated with GDM (as defined by either of the three criteria). In an earlier study done by Rizk *et al*, it was found that gestational diabetes mellitus was not associated with increased risk of urinary tract infections or of maternal and perinatal morbidity as a result of infection[8].

Pre-eclampsia has been associated with gestational diabetes in various studies[7,9,10]. In the hyperglycaemia and adverse pregnancy outcomes (HAPO) study, pre-eclampsia was considered as a secondary outcome and it was found to have a positive association with increasing maternal plasma glucose levels[10]. In a retrospective cohort study performed by Xiong *et al* in Canada, GDM women were found to be at increased risk of presenting with pre-eclampsia[9]. In a study done by the Brazilian gestational diabetes study group, GDM as defined by ADA criteria, predicted a 128% increased risk of pre-eclampsia[7]. Defined by WHO criteria, GDM predicted similar increased risk of pre-eclampsia (94%)[7]. In our study we observed that 11.8% of GDM women (defined by ADA criteria) developed pre-eclampsia compared to 3.0% of normal women and this association was found to be statistically significant ($p = 0.032$). Though both WHO and IADPSG criteria also predicted higher rates of pre-eclampsia in GDM women, the association was not statistically significant ($p = 0.334$ and $p = 0.133$, respectively). Hence GDM, as defined by ADA criteria only, was found to be significantly associated with development of pre-eclampsia, though women with GDM (as defined by WHO or IADPSG criteria) also developed pre-eclampsia more commonly.

It has been observed that women with GDM more frequently undergo caesarean delivery compared to normal women[9,10]. In a study by Xiong *et al*, it was observed that women who had GDM more frequently underwent caesarean delivery compared to normal women[9]. The HAPO study also showed weaker associations between glucose levels and primary caesarean delivery[10]. In our study it was observed that women with GDM (defined by ADA criteria) more commonly underwent caesarean delivery compared to normal women (11.8% compared to 9.7%), but no significant association was found between GDM and caesarean delivery. Caesarean delivery was more commonly seen in women with GDM compared to normal women (12.9% of GDM women underwent caesarean delivery compared to 9.0% of normal women) if WHO criteria was used for diagnosing GDM. But this association was not statistically significant (0.287). By using the IADPSG criteria, it was observed that caesarean delivery was more than 1.4 times more common in normal women compared to women with GDM (10.8% compared to 7.5%). But this association was statistically not significant. The lower frequency of caesarean delivery in women with GDM using IADPSG criteria could be because of inclusion of higher number of women in GDM group which in turn is because of lower cut-off plasma glucose values on OGTT and use of single value for diagnosing GDM compared to ADA criteria. Thus no significant association of caesarean delivery was observed with GDM defined by any of the three criteria, though GDM defined by ADA and WHO criteria predicted increased chances of caesarean delivery in GDM women. Naylor *et al* had observed that, knowledge that the mother has gestational diabetes can increase the chances of caesarean delivery[11].

Macrosomia and higher birth weight of newborn have been associated with gestational diabetes mellitus[7,9,10]. The HAPO study showed associations between increasing levels of fasting, 1 hour, and 2 hour plasma glucose obtained on oral glucose-tolerance testing and birth weight above the 90th percentile[10]. In this study, when associations between maternal glucose level and birth weight were estimated with the use of birth weight as a continuous variable, the difference in mean birth weight between the lowest and the highest glucose categories was in the range of 240 to 300 g[10]. In a study done by the Brazilian gestational diabetes study group, GDM by ADA criteria predicted a 30% increased risk of macrosomia while GDM by WHO criteria predicted a 45% increased risk of macrosomia[7]. Xiong *et al* also found that infants born to mothers with GDM were at higher risk of being macrosomic or large-for-gestational-age[9]. In our study it was observed that the mean birth weight of newborns was almost equal in women with GDM (defined by ADA

criteria) and normal women (2.774 ± 0.438 kg and 2.788 ± 0.500 kg, respectively) and this was not found to be statistically significant (0.882). Using the WHO or IADPSG criteria, women with GDM delivered babies with higher mean birth weight compared to normal women (2.818 ± 0.504 kg compared to 2.778 ± 0.492 kg and 2.807 ± 0.444 kg compared to 2.779 ± 0.512 kg, respectively). But the difference in mean birth weights was not statistically significant. No statistically significant difference was seen in the mean birth weight of newborns between GDM and non-GDM groups (as defined by ADA, WHO or IADPSG criteria), though the mean birth weight of newborns was higher in the GDM group (as defined by WHO or IADPSG criteria) compared to the non-GDM group.

The mean birth weight of newborns in India is 2.8 kg[12]. It has been observed that factors other than maternal glycaemia are also responsible for variation in birth weight of newborn in women with GDM. Other factors implicated in foetal macrosomia include maternal obesity, and high serum concentrations of amino acids and lipids[13-15]. In our study, 91.8% of the women were not obese (BMI < 25 kg/m^2) and this could be the factor responsible for the observed outcome of birth weight. Foetal response to maternal hyperglycaemia is also variable, as evidenced by the differences in the frequency of macrosomia in the infants of women with gestational diabetes who belong to different racial and ethnic groups[16,17]. Silva *et al* observed that neonates born to Native-Hawaiian/Pacific-Islander mothers and Filipino mothers had 4 and 2 times the prevalence of macrosomia, respectively, compared with neonates born to Asian (Japanese and Chinese) and Caucasian mothers[16]. Also, these differences persisted after adjustment for other statistically significant maternal and foetal characteristics. Homko *et al* observed macrosomia in 50% of neonates born to Latino women compared to 19% of neonates born to African-American women, and concluded that the ethnic variation in foetal growth may be due to varying influences of *in utero* growth promoters among these different populations as well as underlying genetic factors[17]. In two earlier studies done in south India by Shefali *et al* and Ramachandran *et al*, it was observed that the prevalence of macrosomia was significantly higher in GDM women compared to non-diabetic women[18,19]. In addition, it was also observed that the birth weight of the baby was dependent on the plasma glucose and the body mass index of the mothers[19]. The observed outcome in our study could be related to difference in ethnicity as well as to lower BMI in the study population.

The criteria for diagnosis of GDM were laid down more than 45 years ago and are still in use, albeit with slight modifications[2,20]. The earliest criteria were actually meant to identify women with high risk of future development of diabetes[21]. Other criteria were derived from criteria used in non-pregnant individuals[5]. These criteria were not necessarily meant to identify pregnancies at high-risk for adverse maternal and foetal outcomes, though the latest IADPSG criteria are based on adverse outcomes observed in the HAPO study[6]. The risk of adverse pregnancy outcomes associated with degrees of hyperglycaemia less severe than overt diabetes is still controversial. Few studies have attributed the adverse outcomes in GDM women to factors more commonly observed in association with GDM such as higher maternal age, obesity, or other medical complications[13,22]. Benefits and cost effectiveness of detecting and treating GDM has not been proved yet. The US Preventive Services Task Force, the UK National Health Service, and the Canadian Task Force on the Periodic Health Examination recommended that there is insufficient evidence to make a recommendation for, or against, screening for GDM[23-25].

It was observed in our study that GDM, defined by ADA criteria only, was associated with adverse pregnancy outcome, i.e., pre-eclampsia. Though WHO and IADPSG criteria labelled 2.8 to 3.4 times women as GDM compared to ADA criteria, both of these criteria failed to predict adverse pregnancy outcomes. Hence, it can be concluded that ADA criteria can be used to diagnose GDM till large studies are available for data on adverse pregnancy outcomes in the Indian population, so that health care providers are not overburdened with a large number of GDM women. The recent IADPSG criteria need to be validated in various population groups before they can be universally accepted for diagnosing and treating GDM.

The findings of this study need to be validated by further studies involving larger number of participants and in different regions of India.

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"It is the mind that makes the body rich."

– William Shakespeare.

ORIGINAL ARTICLE

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Evaluation of renal functions in patients having metabolic syndrome in Asian Indian cohort

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Abstract

Introduction: *A close association has been found between the metabolic syndrome and the risk for developing renal impairment. The present study was designed to study the relationship between chronic kidney disease (CKD) and metabolic syndrome (MS) in a specific Asian Indian cohort as no study of similar nature has been reported from India.*

Methods: *The study was a case-control which was performed on 300 patients (150 each as cases and controls) attending the medical OPD or those admitted in medicine wards of a tertiary care hospital. Metabolic syndrome was defined by using criteria recommended in the revised National Cholesterol Education Program (NCEP) Adult Treatment Panel-3 (ATP-3) guidelines. Glomerular filtration rate (GFR) and microalbuminuria were calculated to assess the renal functions. CKD was defined as GFR less than 60 ml/min and microalbuminuria as urinary albumin-creatinine ratio of 30 - 300 mg/gm in females and 20 - 200 mg/gm in males.*

Results: *A statistically significant ($p < 0.001$) association was observed between MS and CKD (47% vs. 17%) and microalbuminuria (35% vs 7%). Odds ratio for the prevalence of CKD showed a positive association with high blood pressure (BP) (2.108; $p < 0.004$), high blood sugar (2.91; $p < 0.001$) and high triglyceride (TG) levels (2.205; $p < 0.002$). Similarly, microalbuminuria had a positive association with high BP (2.11; $p < 0.013$), high blood sugar (5.101; $p < 0.001$), high TG (2.697; $p < 0.001$) and low HDL (1.762; $p < 0.05$). A progressive increase in the odds for both CKD (0.355, 1.977, 2.411 and 2.757 respectively) and microalbuminuria (0.26, 1.863, 2.162 and 6.735, respectively) was observed with increasing number of components of MS (2, 3, 4 and 5 components respectively). Cox logistic regression (r) of the metabolic syndrome components for CKD was 0.40 and that for microalbuminuria was 0.44.*

Conclusion: *These findings suggest a strong and positive association between metabolic syndrome and risk of chronic kidney disease.*

Keywords: *Metabolic syndrome, chronic kidney disease, microalbuminuria.*

Introduction:

Chronic kidney disease (CKD) is an important, chronic, non-communicable disease epidemic that affects the world, including India. In parallel with the growth in kidney disease, the prevalence of obesity/insulin resistance and impaired glucose metabolism has been increasing rapidly, currently meeting epidemic proportions. These metabolic abnormalities (hypertension, impaired glucose tolerance and dyslipidaemia) together constitute what we call as metabolic syndrome. A close association has been found between the metabolic syndrome and the risk for developing renal impairment, clinically expressed in the form of microalbuminuria or CKD[1]. Although, the most commonly used definition of metabolic syndrome is that recommended by The National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III)[2] but for Asian Indians, due to their unique body composition having less average BMI, waist and hip circumferences and muscle mass in contrast to high body fat, waist to hip ratio, truncal skin folds and abdominal sub-cutaneous fat/intra-abdominal fat, a modified NCEP criteria, i.e., waist circumference $\geq$ 90 cm for men or $\geq$ 80 cm for women[3] was used.

It has been observed in many studies that each element of the metabolic syndrome is not only associated with increased prevalence of CKD and microalbuminuria, but also there exists a graded relationship between the number of components present and the corresponding prevalence of CKD or microalbuminuria[1,4,5,6]. However, no Indian study is available in this regard, as per our knowledge. The present study was therefore proposed to examine the relationship between chronic kidney disease and metabolic syndrome in a specific Asian Indian cohort.

Material and methods

The present study was a case control study and participants were selected from the patients attending the out-patient department of a tertiary care hospital or

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admitted in medical wards. A total of 300 participants (150 cases and 150 controls) were taken. Patients having any of the components of the metabolic syndrome were included in the study. Patients were then divided into two groups – those having three or more than three components of the metabolic syndrome were taken as study group while those having one or two components were grouped as controls.

Exclusion criterion

The following patients were excluded from this study:-

1. Patients less than 20 years of age.
2. Patients with missing measurements for any component of the metabolic syndrome or renal functions.
3. Pregnant or menstruating women
4. Patients with advanced kidney failure, i.e., GFR < 15 ml/min per 1.73 m^2.
5. Patients having urinary tract infections.

Patients fulfilling the above criteria were meticulously examined – including a detailed history regarding smoking and drinking habits; history of hypertension and diabetes, use of anti-hypertensive or anti-diabetic medication, NSAIDs; and physical activity. Height, weight, and waist circumference (rounded to the nearest centimeter) of the patient was measured. Circumferential measurement of the waist was measured midway between the lower rib and the iliac crest. Blood pressure (BP) was measured in a supine position, after 5 min rest, using a calibrated mercury sphygmomanometer. Systolic BP and diastolic BP was recorded as the 1st and 5th Korotkoff sounds, respectively. Blood sample was collected after an overnight fast of 8 hrs for lipids, glucose, creatinine, and other biochemical parameters. All the data was recorded in a specially designed pro forma.

Metabolic syndrome was defined by using criterion recommended in the revised National Cholesterol Education Program (NCEP) Adult Treatment Panel-3 (ATP-3) guidelines[3]. It requires at least three of the following:-

A. Central obesity: waist circumference ≥ 90 cm in males or ≥ 80 cm in females.
B. Triglyceride levels ≥ 150 mg/dl.
C. HDL-C < 40 mg/dl in males, < 50 mg/dl in females.
D. Blood pressure ≥ 130/85 mmHg or treatment of hypertension.
E. Fasting plasma glucose ≥ 110 mg/dl.

Outcome measures

To assess the renal functions of patients with metabolic syndrome, glomerular filtration rate (GFR) and microalbuminuria were analysed. CKD was defined as GFR < 60 ml/min. Nephelometry was used to detect microalbuminuria. Participants were considered to be having microalbuminuria if at least two early morning spot urine samples taken at an interval of three months were having albumin-creatinine ratio in the range of 30 - 300 mg/gm in females and 20 - 200 mg/gm in males.

Statistical analysis

The t-test (unpaired) for mean difference was used for the variables having measurements scale data like height, weight, Hb, etc., and chi-square test was used for nominal or ordinal scale data like current smoking, physical activity, etc. To assess the effect of components of metabolic syndrome on GFR and microalbuminuria, Wald chi-square test was applied in regression model. Odds ratios were considering significant at 95% confidence level if p value ≤ 0.05 and significant at 99% confidence interval, if p valued ≤ 0.01; otherwise non-significant. All this analysis was done by using the statistical software SPSS version-13.

Results

The mean age of study group was 62.07 ± 10.68 years and that in control was 48.47 ± 14.42 years indicating greater likelihood of MS in older age ($p < 0.015$). A female sex predilection was observed in participants with metabolic syndrome. The difference regarding the smoking and drinking habits in cases and controls was non significant ($p > 0.08$ and > 0.121, respectively). The association with physical inactivity was found to be statistically significant ($p < 0.05$). There was a significant ($p < 0.001$) association of metabolic syndrome (MS) with increased waist circumference, weight, basal metabolic index and blood pressure (both systolic and diastolic). However, the difference in height was statistically non-significant ($p > 0.05$). Elevated levels of plasma glucose were significantly associated with the metabolic syndrome. Furthermore, high triglyceride level, low HDL cholesterol level and high VLDL levels had significant association with MS (Table I). On the other hand, LDL levels were not significantly associated with the metabolic syndrome. eGFR was 70.625 ± 34.26 ml/min in MS and 81.45 ± 31.76 for those without MS. In addition, 47% of the MS cases were having CKD as compared to 17% in participants not having the syndrome ($p < 0.001$). Similarly, 35% as compared to 7% of the participants were having microalbuminuria ($p < 0.001$). No significant association of MS was observed with clinical proteinuria (Table I).

Table I: Baseline characteristics of the study participants.

Parameters		Study group (n = 150)	Control group (n = 150)	P
Age (year)		62.07 ± 10.68	48.47 ± 14.42	< 0.015
Sex	Male	67	82	> 0.083
	Female	83	68	
Smoking	Yes	30	43	> 0.08
	No	120	107	
Alcohol consumption	Yes	20	30	> 0.121
	No	130	120	
Physically inactive (%)		80	68.67	< 0.05
Waist circumference (cms)		93.85 ± 12.02	83.83 ± 11.48	< 0.001
Height (cms)		160.81 ± 10.07	162.65 ± 9.03	> 0.097
Weight (kg)		69.41 ± 14.51	61.75 ± 13.96	< 0.001
BMI (kg/m^2)		26.84 ± 5.15	23.34 ± 5.02	< 0.001
Systolic BP (mmHg)		147.44 ± 21.4	135.6 ± 24.15	< 0.001
Diastolic BP (mmHg)		92.27 ± 12.46	86.53 ± 14.59	< 0.001
Waist circumference (cms)		93.85 ± 12.02	83.83 ± 11.48	< 0.001
Fasting blood sugar (mg%)		131.11 ± 66.55	117.11 ± 56.13	< 0.05
Triglycerides (mg%)		200.04 ± 85.61	141.86 ± 71.72	< 0.001
Cholesterol (mg%)		203.11 ± 60.48	185.81 ± 46.27	< 0.006
HDL (mg%)		40.03 ± 5.74	43.7 ± 8.2	< 0.001
LDL (mg%)		115.78 ± 40.37	110.13 ± 37.56	> 0.213
VLDL (mg%)		39.64 ± 16.42	30.23 ± 17.56	< 0.001
Blood urea (mg%)		1.151 ± 0.614	81.45 ± 31.76	> 0.367
Serum creatinine (mg%)		1.151 ± 0.614	1.151 ± 0.588	> 1
eGFR (ml/min)		70.625 ± 34.26	81.45 ± 31.76	< 0.004
Chronic kidney disease (%)		47	17	< 0.001
Microalbuminuria (%)		35	7	< 0.001
Proteinuria (%)		15	14	> 0.84

An increasing trend in the prevalence of CKD and microalbuminuria was observed as the number of components of MS increased. The prevalence CKD was 15.8, 18.3, 44, 49.1, and 55 % corresponding to one, two, three, four, and five components, respectively. Similarly, for microalbuminuria the prevalence was of 5.2, 8.6, 29.33, 32.73, and 60% corresponding to the components increasing from one to five (Fig. 1 and 2). There was a positive association of high blood pressure, high blood sugar, and high triglyceride levels with CKD and microalbuminuria (Table II and III). Abdominal obesity and low HDL levels were however, statistically non-significant (Table II). Further, there was no significant association of microalbuminuria with waist circumference ($p > 0.05$). An increasing odd was found to be associated with increasing number of components of MS. There was a graded relationship between the components of MS and the CKD or microalbuminuria. Cox logistic regression (r) of metabolic syndrome components for CKD was 0.40 and that for microalbuminuria was 0.44 (Fig. 3).

Table II: Odds ratio for chronic kidney disease in metabolic syndrome.

Variables	Odds ratio	Confidence interval	P (unpaired)
High blood pressure (≥130/85 mm Hg)	2.108	(1.269-3.503)	<0.004
Abdominal obesity (WC≥90 cms for males and ≥80 cms for females)	1.506	(0.913-2.483)	>0.108
High blood sugar (Fasting sugar≥110 mg%)	2.91	(1.766-4.797)	<0.001
High triglycerides (≥150 mg%)	2.205	(1.334-3.644)	<0.002
Low HDL (<50 mg% in females and <40 mg% in males)	1.181	(0.724-1.927)	>0.505
Two component	0.355	(0.196-0.644)	<0.001
Three component	1.977	(1.152-3.392)	<0.013
Four component	2.411	(1.327-4.379)	<0.003
Five component	2.757	(1.102-6.896)	<0.025

Table III: Odds ratio for microalbuminuria in metabolic syndrome.

Variables	Odds ratio	Confidence interval	P (unpaired)
High blood pressure (≥130/85 mm Hg)	2.11	(1.164-3.929)	<0.013
Abdominal obesity (WC≥90 cms for males and ≥80 cms for females)	1.564	(0.873-2.802)	>0.131
High blood sugar (fasting sugar≥110 mg%)	5.101	(2.788-9.33)	<0.001
High triglycerides (≥150 mg%)	2.697	(1.476-4.93)	<0.001
Low HDL (<50 mg% in females and <40 mg% in males)	1.762	(0.984-3.155)	<0.05
Two component	0.26	(0.118-0.572)	<0.001
Three component	1.863	(1.021-3.399)	<0.041
Four component	2.162	(1.129-4.14)	<0.018
Five component	6.735	(2.619-17.323)	<0.001

Discussion

CKD is increasingly emerging as a major public health problem, associated with poor outcomes and high cost. Therefore, more stress is now being laid to shift the paradigm from curative to preventive strategy. This requires a clear understanding of antecedent risk factors and appropriate treatment for population at risk. Among the risk factors, MS is increasingly being associated with renal function derangement and resultant chronic kidney disease[1].

Greater prevalence of metabolic syndrome in the older age group population is strengthened by the

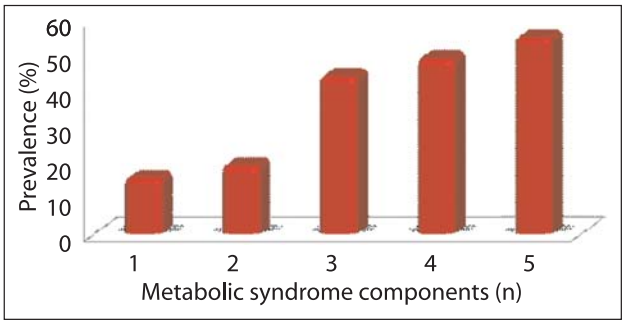

***Fig. 1:** Prevalence of CKD vs. number of metabolic syndrome components.*

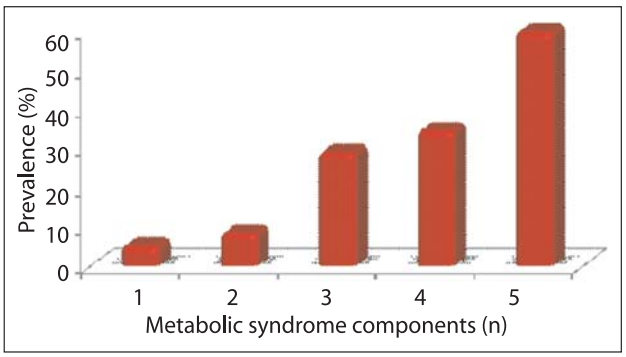

***Fig. 2:** Prevalence of microalbuminuria vs. number of metabolic syndrome components.*

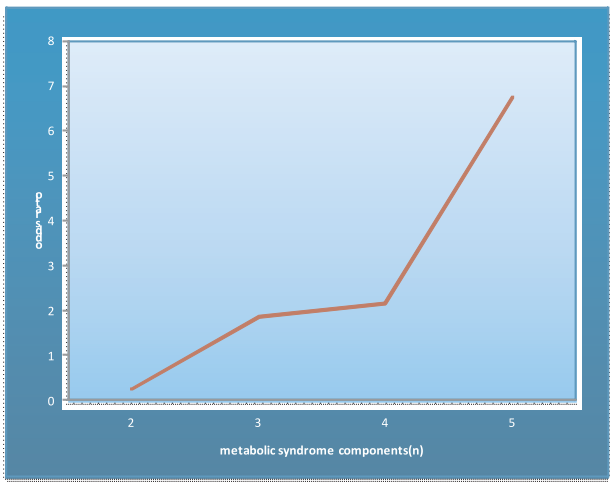

***Fig. 3:** Line diagram depicting the association of prevalence of microalbuminuria with more than one component of the metabolic syndrome.*

statistically significant observation found in our study. The third National Health And Nutrition Examination Survey (NHANES[222]) have already documented that the prevalence of MS in the US population ≥ 20 yr of age is 23.7%[7], rising to ≥ 40% in those ≥ 60 yrs of age[8]. The female sex preponderance as observed by us suggests a high prevalence of abdominal obesity and excess body fat associated with dyslipidaemia and hypertension in Asian Indian women[9,10]. These metabolic perturbations were found particularly common in post-menopausal Asian Indian women. Significant difference in smoking and drinking habits in the study group negates the confounding effect, if any, of these variables in this study.

A strong association of MS was observed with waist circumference, body weight, BMI, systolic and diastolic BP and high blood sugar levels. A significant association of the syndrome with increased lipids is in favour of the concept of atherogenic dyslipidaemia[11,12]. The study identified a strong positive and significant relationship between MS and risk for CKD and microalbuminuria which corroborates the findings observed in studies performed in other countries[1,4-6,13]. The estimated GFR was found to be lower in patients with metabolic syndrome.

Hoehner *et al*[13] correlated the MS profile and microalbuminuria in a cross-sectional study of American Indians from Wisconsin and Minnesota and concluded that individuals with three or more metabolic syndrome traits had a 2.3-fold increased odds of having microalbuminuria compared with a control group without the syndrome. The study by Chen *et al*[1] in the US population concluded that not only was each element of MS associated with increased prevalence of CKD and microalbuminuria, but also there was a graded relationship between the number of components present and the corresponding prevalence of CKD or microalbuminuria ($p < 0.001$ for each). In a Japanese cohort study[5], after 5 years of follow-up, the risk for new CKD in people with MS was significantly higher than in the people without the syndrome. Similar results were reported by Rashidi *et al*[6] in a relatively small sample from Iran, and by Kitiyakara *et al*[4] in South-East Asia.

The study also probes the association of individual components of MS with the odds ratio for the prevalence of CKD and microalbuminuria. The observation suggests a mixed response. Although high blood pressure, high fasting blood sugar and high triglycerides were significantly associated with both CKD and microalbuminuria, low HDL levels were only associated with microalbuminuria while increased waist circumference, i.e., abdominal obesity was not associated with either of the two. This controversial observation may be due to the reason that the prevalence and impact of each component of MS may vary substantially between different ethnic groups. While in the US population[1], each component was significantly associated with risk of CKD and all the components, except reduced HDL cholesterol, were significantly associated with risk of microalbuminuria; in South East Asian cohort[4], only high BP, high triglyceride and high fasting glucose showed a statistically significant association with risk of CKD.

Several lines of evidence suggest that dyslipidaemia may be an important factor for the development and progression of CKD[14,15]. In the modification of diet in renal disease (MDRD) study, low HDL cholesterol independently predicted renal disease progression in 840 patients[14]. In the atherosclerosis risk in community study of 12,000 subjects, Muntner *et al*[15] observed that high triglycerides increased whereas high HDL cholesterol decreased the probability of developing renal dysfunction. Similar association of risk of CKD and microalbuminuria was observed with triglycerides in this study. Although reduced HDL cholesterol was found to be significantly associated with microalbuminuria, the result was not significant for association with CKD. Similar observations were reported in the large scale study[4] in South-East Asian cohort.

Reports have confirmed the presence of proteinuria and glomerulomegaly in obesity, often with FSGS, but this role of obesity as a risk factor for CKD has not been a consistent finding. In the US and Japanese population[1,16], obesity was found as an independent risk factor for chronic kidney disease and microalbuminuria. On the contrary, in the study on South-East Asian cohort[4], obesity was not associated with CKD. They ascribed the result to the lower number of obese patients and the lower degree of obesity as the criteria used for waist circumference in the South-East Asian study was modified NCEP criteria. The results of this study also did not support the association of increased waist circumference with the metabolic syndrome. Use of modified NCEP criteria in both the studies seems to be the underlying cause leading to the drift from the expected result. However, the effect of obesity on renal deterioration cannot be negated and needs further large scale trials.

The novelty and strength of this study is that the effect of additive number of components of MS with the prevalence of CKD and microalbuminuria were analysed. It was clearly seen that a gradient relationship existed between the components of MS and the corresponding prevalence of CKD or microalbuminuria. Furthermore, the odds ratio for the prevalence of CKD and microalbuminuria also showed a similar increasing association with increasing number of MS components

as reported in earlier studies[1,4]. All these findings are an indirect indicator of the adverse effect on the renal functions in patients with MS. However, this study does not establish a cause and effect relationship. There are two other major limitations of this study – first, the study is a cross-sectional study; and second, it involves a small sample of subjects.

This calls for the need of further large scale trials on this subject – particularly as this is an important issue in the current scenario in the developing countries like India where MS and CKD are both increasing at an alarming rate. Also, it needs to be established if timely intervention in these high-risk groups will alter the prevalence of CKD and microalbuminuria.

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"Mistakes are the portals of discovery."

– JAMES JOYCE.

ORIGINAL ARTICLE

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Clinical profile of psychotic disorders in the elderly: A retrospective study

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Abstract

Background: Much about psychotic disorders in the elderly remains obscure due to exclusion of this age group in a majority of studies. However, as the population ages, this problem is expected to increase. The study was conceived with the aim of assessing the clinical profile of psychotic disorders in the elderly.

Settings: Psychiatry out-patient department of a teaching hospital in Northern India.

Design: Retrospective chart review.

Material and methods: The sample comprised of all the patients with psychosis who were 60 years or older. Data pertaining to socio-demographic details and clinical features were obtained from the medical records and analysed using descriptive statistical methods. The patients with onset of psychosis before 60 years of age were compared with those who developed psychosis after or at the age of 60 years using Chi-square analysis.

Results: A total of 72 patients met the inclusion criteria. The most common diagnosis was schizophrenia (40%) followed by bipolar disorder (30.5%). Family history of psychiatric illness was present in 34.7% of the sample, out of which psychosis NOS (12.5%) was the most common diagnosis. When compared to patients with onset before 60 years, those with onset after 60 years had higher frequency of precipitating factors and co-morbid medical illness and lesser frequency of psychiatric illness in the FDRs.

Conclusion: There is an ever increasing need to study the psychotic disorders in elderly as a distinct clinical entity. Future research could pave the way for better preventive and management strategies for psychosis in this vulnerable age group.

Key words: Psychosis, elderly, schizophrenia, late-onset psychosis.

Introduction

Psychotic disorders in the elderly can either be disorders which develop late in life, or chronic conditions continuing from the younger age. These conditions have not been extensively studied, given the fact that majority of the studies on psychotic disorders have excluded the elderly group[1]. There is confusion regarding the nosological status of late onset psychotic illness. Although it formed a separate diagnostic category in ICD-9 and DSM-III R, the more recent versions, ICD-10 and DSM-IV TR classify such conditions under schizophrenia[2] (provided they meet the criteria for schizophrenia), regardless of the age of onset. However, a consensus statement of the international late onset schizophrenia group stated that there is a strong epidemiological evidence for the cut-off age of 60 years to define the very late-onset schizophrenia like psychosis[2]. With this background, the study was conceived to assess the clinical profile of psychotic disorders in the elderly, in order to better understand the condition.

Material and methods

This was a retrospective study conducted at the psychiatry out-patient department of a tertiary care teaching hospital in Northern India. The hospital caters to a large population from North-eastern India and Nepal. The sample comprised of all the patients who were 60 years or older and had clinical features suggestive of 'Psychosis' as per ICD-10[3] during the period of three years from January 2006 to December 2008; and all the cases were further sub-classified according to DSM IV TR[4]. Data pertaining to socio-demographic details, history of presenting illness, past history, family history, co-morbid medical illnesses, psychiatric diagnoses, and other details were obtained from the medical records and analysed using descriptive statistical methods.

For the purpose of assessing the possible differences in clinical features depending on the age of onset, the patients with onset of psychosis before 60 years of age (Group A) were compared with those who developed psychosis after or at the age of 60 years (group B) using Chi-square analysis.

Results

A total of 72 patients met the inclusion criteria out of which 45 (62.5%) were males and 27 (37.5%) were females.

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Majority of the patients (n = 44, 61%) hailed from rural background. The age of the sample ranged from 60 to 85 and the mean age was 66 years.

Diagnostic break-up

The DSM-IV TR[4] was the diagnostic system routinely used to diagnose patients. Schizophrenia (n = 29, 40%) was the most common diagnosis, followed by Bipolar disorder (n = 22, 30.5%), schizophreniform disorder (n = 6, 8.3%) and psychosis not otherwise specified (n = 5, 6.9%). The diagnostic break-up of the sample is listed in Table I.

Table I: Diagnostic break-up of the sample.

Psychiatric diagnosis	N	%
Schizophrenia	29	40.3
Bipolar disorder	22	30.5
Schizophreniform disorder	6	8.3
Psychotic disorder NOS	5	6.9
Brief psychotic disorder	3	4.2
Dementia	3	4.2
MDD	2	2.8
Schizoaffective disorder	1	1.4
Delusional disorder	1	1.4

Precipitating factor

Any life event that triggered the onset of illness was considered a precipitating factor. A total of 14 patients (19.4%) were reported to be having a precipitating factor for their illness, while the other 58 (80.6%) did not have a triggering factor.

Medical co-morbidity

Table II enlists the various co-morbid medical conditions which were present in 41% (n = 30) of the patients. Hypertension was the most common medical illness (n = 14, 19.2%), followed by diabetes mellitus (n = 6, 8.3%) and sensory impairment (n = 5, 7%).

Family history

History of psychiatric illness in first degree relative (FDR) was present in 34.7% (n = 25) of the sample (Table III). Among the FDRs, psychosis not otherwise specified (n = 9, 12.5%) was the most common diagnosis, followed by bipolar disorder (n = 8, 11.1%) and schizophrenia (n = 5, 6.94%).

Table II: Medical co-morbidity in the sample.

Medical illness	N	%
Hypertension	14	19.2
Diabetes mellitus	6	8.3
CVA	3	4.2
Bronchial asthma	3	4.2
Hearing impairment	3	4.2
Cataract	2	2.8
Osteoarthritis	2	2.8
Others	5	6.9

Table III: Psychiatric co-morbidity in the FDRs of sample.

Diagnosis	N	%
Psychotic disorder NOS	9	12.5
Bipolar disorder	8	11.1
Schizophrenia	5	6.9
Brief psychotic disorder	1	1.4
Dementia	1	1.4
OCD	1	1.4
Total	25	34.7

Intergroup comparison according to age of illness onset (Table IV).

Table IV: Comparison between Group A (onset of psychosis before 60 years) and Group B (onset of psychosis at or after 60 years)

Clinical feature		Group A (N = 40)		Group B (N = 32)		p
		n	%	n	%	
Sex	Male	22	48.9	23	51.1	0.142
	Female	18	66.7	9	33.3	
Domicile	Rural	26	59.1	18	40.9	0.449
	Urban	14	50.0	14	50.0	
Precipitating factor	Present	5	35.7	9	64.3	0.096
	Absent	35	60.3	23	39.7	
Co-morbid medical illness	Present	12	40.0	18	60.0	0.025
	Absent	28	70.0	14	30.0	
Psychiatric morbidity in FDRs	Present	21	84.0	4	16.0	0.0004
	Absent	15	40.4	28	59.6	

When the two groups were compared, there was no significant difference in age, sex, and domicile of the

patients. Patients in group B were reported to have had a precipitating factor more often than those in group A, but the difference was not statistically significant (p = 0.09). However, the patients in group B had significantly higher frequency of co-morbid medical illness (p = 0.025) and lesser frequency of psychiatric morbidity in the FDRs (p = 0.0004).

Discussion

This study is an attempt to assess the clinical profile of elderly patients with psychotic disorders at a tertiary care teaching hospital in Northern India, which caters to a huge population hailing from eastern Uttar Pradesh, Bihar, Madhya Pradesh, and Nepal. As the elderly group has been excluded from most of the studies on psychosis[1], data pertaining to this particular age group is sparse, more so in the Indian context.

There was no significant difference in the gender distribution of the sample in this study. This finding is not in agreement with most of the previous data, which have reported female preponderance[5-10]. Researchers have postulated that oestrogen-mediated dopaminergic inhibition may protect younger women from schizophrenia. However, some authors stated that this may be unlikely as there is usually a time lag of several years between the menopause and onset of psychosis[11-12]. Also, since majority of the sample was from rural areas, it is possible that elderly men were taking professional help more readily than elderly women, thus neutralising the gender disparity seen in other studies.

In our study, the patients with late onset were found to have higher frequency of precipitating factors and lesser frequency of FDRs with psychiatric morbidity. This compares well with the previous reports[2,6,13,14], which have similar findings. The presence of precipitating factors points to the greater role of environment in the causation of psychosis in the elderly. It can be reasonably inferred that, by avoiding the precipitating factors, we can prevent the occurrence of psychosis in at least a subset of elderly patients. Genetic loading has lesser influence on the causation of psychosis in the elderly as indicated by significantly lesser frequency of psychiatric morbidity in the FDRs.

Patients with very late age of onset were found to have higher frequency of co-morbid medical illness. This finding is in concordance with previously available data[11,12,14]. This association has two major implications, namely, possible aetiological linkage in at least a fraction of the elderly with psychotic disorders and the need to consider drug interactions and pharmacodynamic factors while managing the psychosis with psychotropic medication. Studies have also shown an association between sensory impairment and late-onset schizophrenia[11,15-18]. Sensory impairment, if any, should be managed appropriately as it may worsen the psychotic features in the elderly[11,15].

The major limitations of the study are its retrospective design and inclusion of all elderly patients with psychotic features, irrespective of psychiatric diagnosis. Further work with a larger, more homogenous sample group is necessary to explore the clinical features in greater detail.

Conclusion

The patients with onset of psychosis after 60 years of age had significantly higher frequency of co-morbid medical illness and lesser frequency of psychiatric illness in FDRs. Psychotic disorders in the elderly are evidently understudied because of the propensity of the researchers to exclude this age group from most studies. The need to study such disorders in the elderly as a distinct clinical entity is of utmost importance due to varied clinical presentation and age-related biological changes. The findings, on one hand, could pave the way for integrated treatment approach incorporating the biological, psychological, and social aspects; and on the other hand, may help devise strategies to prevent psychosis in this vulnerable age group. The differences between early-onset and late-onset psychosis, and possible relationships to medical illnesses and sensory deficits, needs further investigation to conclude if psychosis in the elderly could possibly be predicted and prevented.

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ORIGINAL ARTICLE

JIACM 2015; 16(1): 43-6

Iatrogenic Cushing's syndrome – An observational study

Saurabh Srivastava, Sohaib Ahmad**, Minakshi Dhar**, Ajai Kumar Garg****

Abstract

Introduction: *The use of glucocorticoids is very common for various inflammatory, autoimmune, and neoplastic disorders. The use of these drugs may lead to iatrogenic Cushing's syndrome which is the most common form of hypercortisolism in clinical practice.*

Material and methods: *The patients presenting to the hospital with the features of Cushing's syndrome were enrolled for the study. A detailed history and clinical examination was carried-out in each study subject according to a pre-structured protocol. The details regarding use of corticosteroids and their indication of use were also recorded.*

Results: *A total of eighty-two patients were enrolled for the study over a period of one year. The females outnumbered the males. The most common prescription of steroid therapy was joint pain followed by respiratory diseases. The most common clinical features of iatrogenic Cushing's syndrome were moon facies followed by increase in dorso-cervical and supraclavicular fat leading to buffalo hump.*

Conclusion: *Iatrogenic Cushing's syndrome is not uncommon. Glucocorticoids are widely prescribed drugs; but if used irrationally, troublesome adverse effects may be noted.*

Introduction

Glucocorticoids are often prescribed for various inflammatory, autoimmune, and neoplastic disorders. The occurrence of iatrogenic and factitious Cushing's syndrome is therefore a distinct possibility in clinical practice. It is more common with oral therapy; however, other forms of glucocorticoid delivery also have the potential to cause Cushing's syndrome.

The glucocorticoids were first used for therapeutic purpose in 1948 in a case of severe rheumatoid arthritis. Immediately, however, the potential adverse effects of exogenous steroid administration became evident[1]. Cushing's syndrome resulting from exogenous glucocorticoids now is a well-recognised and documented entity. Iatrogenic (exogenous) Cushing's syndrome is the most frequently observed form of hypercortisolism in the clinical practice[2,3].

It may appear following the treatment of many diseases where the anti-inflammatory, immunosuppressive, and apoptosis-inducing effects of glucocorticoids are exploited (e.g., autoimmune, haematologic, inflammatory diseases). About 1% of the general population are long-term users of systemic glucocorticoids[4,5] and about two-thirds exhibit iatrogenic manifestations related to excessive exposure to glucocorticoids[6]. The situation is further compounded by the irrational uses of these drugs.

The present study was planned to assess the occurrence of iatrogenic Cushing's syndrome, as well as the factors responsible for the same. Clinical features in these cases have also been studied.

Material and methods

Consecutive patients presenting to the tertiary care centre with the features of Cushing's syndrome were enrolled for the study for a period of one year.

The diagnosis of drug-induced Cushing's syndrome was made by measuring the fasting serum cortisol levels, well-documented clinical features, as well as history of taking oral steroids in any form of medicine, i.e., allopathic, ayurvedic, unani, or any other form of alternative medicine. The patients who were having higher cortisol levels above the normal range were excluded from the study and only those patients having cortisol levels < 5 mcg/dl or below 15 mcg/dl were included in the study.

Patients with cortisol values < 5 mcg/dl required oral corticosteroids in physiological dose, i.e., 7.5 mg in divided doses with a higher dose in the morning, i.e., 5 mg to overcome the symptoms of secondary Addison's disease due to inadequate cortisol levels in blood secondary to hypothalamic-pituitary axis suppression. A detailed history and clinical examination regarding use of corticosteroids, occupation, family details, blood pressure recording, and fasting blood glucose values were carried-out in each study subject according to a pre-structured protocol. The demographic and anthropometric profiles of all the patients were also recorded.

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A thorough and detailed history was obtained regarding the corticosteroid intake, stating the duration and indication.

Results

A total of eighty-two patients were enrolled for the study over a period of one year. The females outnumber the males in the use of exogenous steroids. The detailed demographic profile of the patients is shown in Table I.

Table I: Demographic profile of patients presenting with Iatrogenic Cushing's syndrome.

S no	Demographic characteristics	Values
1.	Age	45.24+10.01
2.	Sex	M:F = 14:68 (1:4.8)
3.	Height	154.04+7.99
4.	Weight	65.39+13.89
5.	BMI	27.45+5.18
6.	Systolic blood pressure	132.58+16.5
7.	Diastolic blood pressure	81.90+7.23
8.	Haemoglobin	11.57+1.77
9.	Total leucocyte count	9407+2683
10.	ESR	41.97+21.70
11.	Serum creatinine	0.85+0.16

The patients were started on steroids for various indications. The most common indication for steroid therapy was joint pain followed by respiratory diseases. The details regarding the indication of starting steroids are shown in Table II. The most common clinical presentation of iatrogenic Cushing's syndrome was moon facies followed by an increase in dorsocervical and supraclavicular fat leading to buffalo hump. Table III shows the clinical presentation of the patients presenting with iatrogenic Cushing's syndrome. Fig. 1 depicts the physical appearance of a patient presenting with the disease.

Table II: Indications for starting steroids.

S no	Indications	Values (n = 82)	Percentage
1.	Joint pains	40	48.7
2.	Respiratory diseases	22	26.8
3.	Dermatologic diseases	7	8.5
4.	Generalised body ache	8	9.7
5.	Connective tissue diseases	7	8.5
6.	Gastrointestinal diseases	5	6.0

Table III: Clinical presentation of patients with Iatrogenic Cushing's syndrome.

S no.	Presentation	Number (n = 82)	Percentage
1.	Buffalo hump	65	79.2
2.	Moon facies	76	92.6
3.	Ecchymosis (easy bruising)	10	12.1
4.	Striae	4	4.8
5.	Hypertension	14	17.0
6.	Hyperglycaemia (including diabetes)	10	12.2
7.	Cataract	8	9.7

The cortisol values of the paients are shown in Fig. 2 in which the patients were divided in three groups as per the cortisol values. The results also depicted that the value of cortisol is not dependent upon the dose or nature of steroid; however, it was found that the values are dependent upon whether the patient is presently on steroids; or if the patient is not on steroids, then the steroid-free interval prior to consultation.

Discussion

Iatrogenic Cushing's syndrome is the most common form

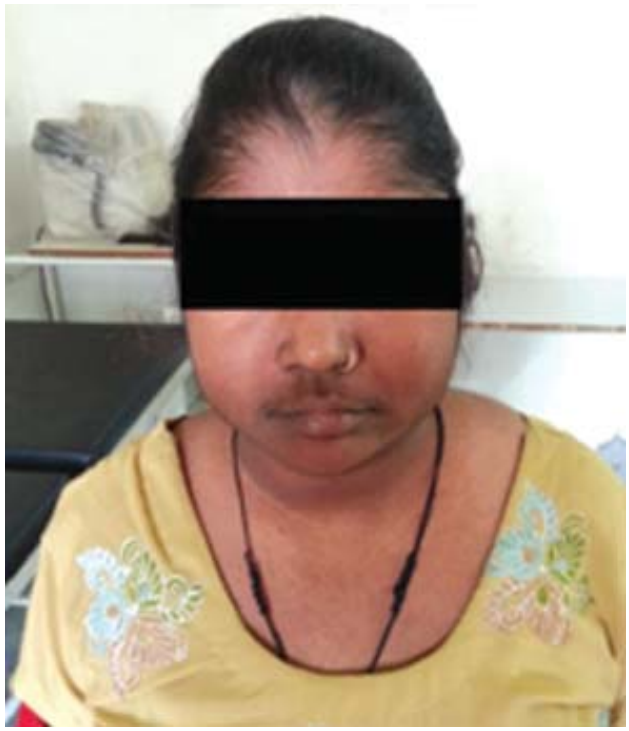

Fig. 1: *The presentation of a patient with Iatrogenic Cushing's.*

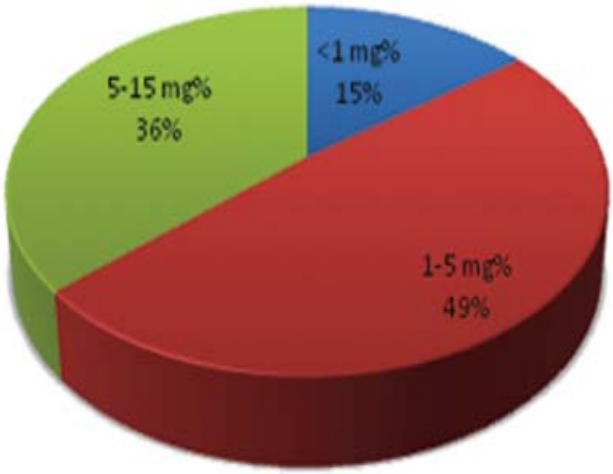

Fig. 2: *A Pie chart showing cortisol values in patients with Iatrogenic Cushing's Syndrome.*

of hypercortisolism[2,3]. About 1% of the general population are long-term users of systemic glucocorticoids[5] for the treatment of various diseases, often in very high doses that sometimes lead to the development of severe hypercortisolism. About two-thirds of these exhibit iatrogenic manifestations related to excessive exposure to glucocorticoids[6].

The present study demonstrated that the occurrence of iatrogenic Cushing's syndrome in clinical practice is not infrequent. It is more commonly seen in female patients. The common indications for steroid treatment in the present study were joint disorders, followed by respiratory diseases. The other indications were connective tissue diseases, dermatologic diseases, and gastrointestinal disorders. However, a study done in the United Kingdom suggested that the commonest indication was respiratory diseases followed by dermatologic, joint, neurological, gastrointestinal, and neoplastic disorders[5].

Iatrogenic hypercortisolism is unique, as the use of exogenous glucocorticoids will induce two disorders in the subject; first is the presence of symptoms specific of Cushing's syndrome due to hypercortisolism, and secondly features of Addison's disease-like syndrome on sudden withdrawal due to the suppression of the endogenous hypothalamic-pituitary-adrenal axis. The patient might not be aware of this phenomenon and may develop severe symptoms which can be life-threatening on intermittent self-withdrawal of the drug.

It is worthwhile to know the clinical presentation and aetiology of endogenous Cushing's syndrome. The study from a premier institute of the country has shown Cushing's disease as the commonest cause of endogenous Cushing's syndrome. Age of presentation in the series was around 27 yrs with female preponderance. Commonest presenting complaints were hypertension and diabetes mellitus. Other features were hirsutism, obesity, myopathy, striae, psychiatric manifestation, and menstrual irregularities (in females)[7].

Three major type of complications can be associated with glucocorticoid withdrawal: first, reactivation of the underlying disease: second, secondary adrenal insufficiency; and third, steroid withdrawal syndrome.

The clinical picture of iatrogenic hypercortisolism is similar to endogenous Cushing's syndrome but with some differences. Hypertension is frequent, but hypokalaemia occurs less commonly due to poorer mineralocorticoid activity of synthetic glucocorticoids[8]. Virilisation and hirsutism are also less frequent, as the exogenous steroids diminish the production of adrenal androgens by inhibiting endogenous ACTH (corticotropin) secretion. On the other hand, glaucoma and other ophthalmological complications, e.g., posterior subcapsular cataract[9], avascular necrosis of bone[10], and benign intracranial hypertension[11] occur more often. Osteoporosis is one of the major side-effects of glucocorticoid therapy. Calcium, vitamin-D supplementation, and bisphosphonates can be prescribed to the patients requiring long-term glucocorticoid therapy, even at the beginning of steroid therapy as a primary prevention[12].

The present study demonstrated that Cushingoid appearance with moon facies, buffalo hump, and centripetal obesity are the most common presenting complaints; however, straie are not so frequent. The presence of cataract, hypertension, and hyperglycaemia although seen in the present study were not so frequent.

Any drug-induced disease should be treated with the omission of the drug; however, this strategy cannot be used in these cases due to the insufficiency of the endogenous HPA axis, and sometimes the underlying disease requiring steroid therapy. A sudden withdrawal of glucocorticoid therapy would lead to the reactivation of the underlying disease as well as appearance of secondary adrenal insufficiency.

Conclusion

Thus it can be concluded from the present study that iatrogenic Cushing's syndrome is not uncommon. Corticosteroids are useful drugs, if prescribed for an evidence-based indication; but if used irrationally, troublesome adverse effects may be noted. The corticosteroids should be used for a specific indication, a proper duration, and with an appropriate dosage schedule. The risk – benefit ratio should be evaluated

before starting therapy. The physicians must also explore the alternative modes of treatment of various diseases, where steroids are indicated as primary drugs, and these alternative modalities may be used, if troublesome side-effects appear following glucocorticoid treatment and warrants discontinuation of the same.

Limitations of the study

1. **The short synacthen stimulation test was not performed for the diagnosis of secondary Addison's disease.**
2. **Follow-up data of the patients is rather inadequate.**

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"Hatred is toxic waste in the river of life."

– MICRON.

UPDATE ARTICLE

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Newer insight in the management of hyponatraemia: role of acquaretics/vaptans

Mujahid Beg, Imran Rizvi***

Introduction

Hyponatraemia is the most common electrolyte abnormality seen in hospitalised and critically ill patients. It is seen in 15 - 30% of hospitalised patients[1,2]. Hyponatraemia has been shown to be an independent predictor of mortality in the intensive care unit[3]. Even mild asymptomatic hyponatraemia has been shown to be associated with attention impairment, falls, fractures and osteoporosis in elderly patients[4,5]. Conventional management of hyponatraemia includes step-by-step management starting from water restriction in mild cases to administration of saline in symptomatic cases. A major new development in the management of hyponatraemia is the use of vaptans or acquaretics. Vaptans are arginine vasopressin (AVP) receptor antagonists that act by directly inhibiting the effect of increased AVP which results in excretion of electrolyte-free water. In this article we will summarise the diagnostic approach to hyponatraemia, conventional treatment of hyponatraemia, as well as future perspective in the management of hyponatraemia including the role of acquaretics/vaptans.

Clinical features

Acute hyponatraemia (defined as hyponatraemia developing within 48 hours) causes lethargy, confusion, psychosis, reversible ataxia. When severe, it can also cause seizures, coma, and respiratory arrest[6]. Chronic and mild hyponatraemia can be asymptomatic, or it can present with cognitive impairment, falls, and weakness.

Diagnostic approach and causes of hyponatraemia

Falsely low sodium levels can be seen in the setting of hyperlipidaemia and hyperproteinaemia. These falsely low sodium levels are referred to as pseudohyponatraemia. This pseudohyponatraemia is a benign finding and must be excluded before further work-up. Presence of osmotically active substances like glucose or mannitol can also cause hyponatraemia; but hyponatraemia in this case has high serum osmolarity.

Hyponatraemia with low serum osmolarity (hypo-osmolar hyponatraemia) can occur in the setting of decreased extracellular (ECF) volume (hypovolaemic hyponatraemia), it can occur in the setting of normal ECF volume (euvolaemic hyponatraemia), or it can occur in the setting of increased ECF volume (hypervolaemic hyponatraemia).

Another important evaluation apart from serum osmolarity and ECF volume status is the measurement of urinary osmolarity. If urinary osmolarity is < 100 mOsm/l then cause of hyponatraemia can be excessive water intake, reset osmostat, or low solute intake.

In hypovolaemic hyponatraemia there is decrease in both total body sodium and water leading to ECF volume depletion with consequent AVP release and decreased solute-free water excretion. Clinically, the patient will have tachycardia, orthostatic hypotension, and loss of skin turgor. Causes of hypovolaemic hyponatraemia can be further classified into extra-renal and renal causes. Extra-renal causes include vomiting, diarrhoea, burns, peritonitis, and pancreatitis, etc. Renal causes include use of thiazide diuretics, mineralocorticoid deficiency, and salt wasting nephritis. Extra-renal and renal causes can be differentiated with the help of estimating urinary sodium. If urinary sodium is less than 10 mmol/l then this points towards an extra-renal cause; and if urinary sodium is more than 20 mmol/l, it points towards a renal aetiology of hyponatraemia.

Prototype example of euvolaemic hyponatraemia is the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). In this syndrome there is hyponatraemia along with hypo-osmolarity, physical examination does not show any signs of dehydration or fluid overload, urinary osmolarity is > 100 mOsm/l and urinary sodium is > 25 mmol/l. But disorders like hypoparathyroidism, hypopituitarism, and adrenal insufficiency must be ruled-out before making the diagnosis of SIADH. Causes of SIADH include neoplastic, vascular, infectious and inflammatory disorders of central nervous system (CNS) and respiratory system. Drugs like SSRIS, tricyclic antidepressants, carbamazepine, desmopressin and oxytocin can also cause SIADH.

Causes of hypervolaemic hyponatraemia include cardiac failure, liver cirrhosis, and nephrotic syndrome. In these

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conditions decreased effective arterial blood volume leads to activation of renin-angiotensin-aldosterone (RAAS) system and increased AVP levels leading to retention of fluid in excess to sodium.

An algorithm for the diagnostic approach to hyponatraemia is shown in Fig. 1.

Conventional treatment of hyponatraemia and its disadvantages

Hyponatraemia in hypovolaemic patients is treated with infusion of normal saline. The options for treatment of euvolaemic hyponatraemia and hypervolaemic hyponatraemia are fluid restriction, 3% saline administration, and use of loop diuretics. For fluid restriction to be effective, the daily fluid intake should be less than urinary output plus daily insensible losses[7]. Water restriction is slow to work and difficult to sustain due to inherent increased thirst sensation in these patients resulting in poor compliance[8]. Saline administration can also be problematic in patients with hypervolaemic hyponatraemia as it can further cause volume expansion[8]. Also, patients with hyponatraemia of > 48 hours duration are at an increased risk of developing central or extra-pontine myelinolysis if serum sodium is corrected at a rate of > 12 mmol/l/day[8,9]. Loop diuretics are effective in hypervolaemic patients but they can lead to volume depletion[7]. Demeclocycline – a tetracycline antibiotic – has been used to treat chronic hyponatraemia as it causes AVP resistant diabetes insipidus-like state[10]. The main disadvantage of demeclocycline is nephrotoxicity especially in the presence of liver diseases and congestive heart failure[7,11]. Lithium can also increase sodium levels

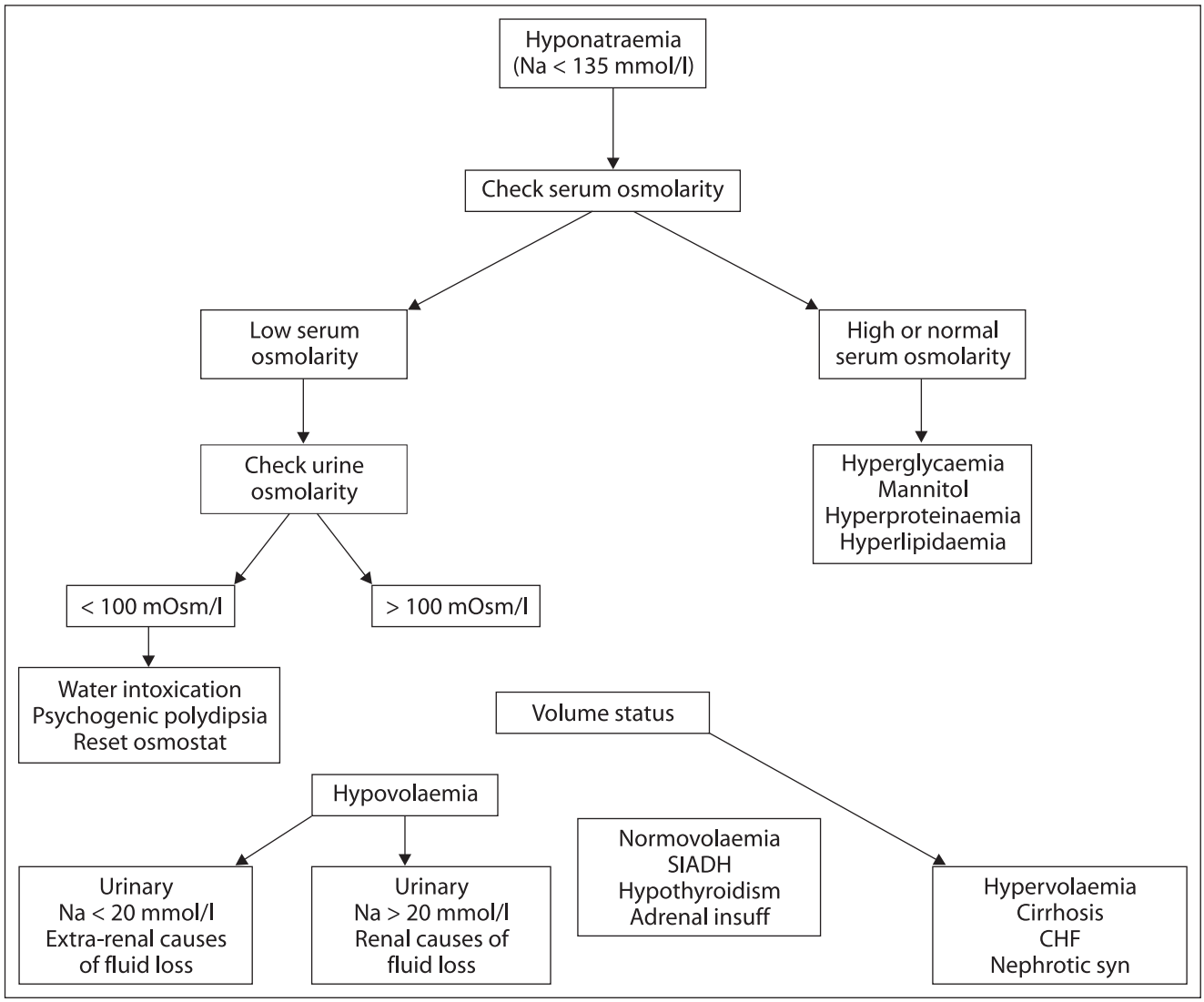

***Fig. 1:** Algorithm for the diagnostic work-up of hyponatraemia,*

by creating a diabetes insipidus-like state, but lithium has a very narrow risk benefit ratio and an array of adverse effects[7].

Role of vaptans/acquaretics in management of hyponatraemia

Vaptans are vasopressin receptor antagonists. They act by increasing electrolyte-free water excretion, and thereby increasing serum sodium concentration. Recently, non-peptide antagonists to V2 vasopressin receptor have been developed.

There are specific non-peptide antagonists namely tolvaptan, lixivaptan and satavaptan, as well as dual V1/V2 receptor antagonist namely conivaptan[12]. But out of these agents only conivaptan and tolvaptan are approved so far by the US Food and Drug Administration (FDA). Conivaptan is approved for intravenous use in hospital settings for the treatment of euvolaemic and hypervolaemic hyponatraemia[7]. Velez *et al* conducted a retrospective study on 18 patients of SIADH who were treated with intravenous conivaptan. They found that twenty-four hours after initiation of therapy, all patients had at least a 3 mmol/l increase in serum sodium, with 66.7% (12/18) of the patients having an absolute increase > or = 4 mmol/l, urine osmolality decreased in all patients with a mean reduction of 45.9 ± 28.8% from baseline[13]. They therefore concluded that intravenous conivaptan is an effective aquaretic to treat hyponatraemia caused by SIADH[13].

Tolvaptan is an orally active selective V2 receptor antagonist. It is approved for the treatment of euvolaemic and hypervolemic hyponatraemia. In two multicenter, randomised, double-blind, placebo-controlled trials (the study of ascending levels of tolvaptan in hyponatraemia, SALT-1 and SALT-2), the efficacy of tolvaptan was evaluated in patients with euvolaemic or hypervolaemic hyponatraemia. It was found that serum sodium concentrations increased more in the tolvaptan group than in the placebo group during the first 4 days ($p < 0.001$) and after the full 30 days of therapy ($p < 0.001$). The condition of patients with mild or marked hyponatraemia improved ($p < 0.001$ for all comparisons). During the week after discontinuation of tolvaptan on day 30, hyponatraemia recurred[14].

Role of vaptans in SIADH

In a recent study, hyponatraemic patients in the SALT-1 and SALT-2 studies with a diagnosis of SIADH were identified based on clinical diagnosis by individual study investigators. Subjects were randomised to receive oral placebo (n = 52) or tolvaptan 15 mg daily, with further titration to 30 and 60 mg daily, if necessary, based on the response of serum sodium (n = 58). It was found that In patients with SIADH, improvement in serum sodium was significantly greater ($p < 0.0001$) with tolvaptan than placebo over the first 4 days of therapy as well as the entire 30 day study, with minimal side-effects of increased thirst, dry mouth, and urination. Only 5.9% of tolvaptan-treated patients had overly rapid correction of hyponatraemia as defined by current guidelines. After discontinuation of tolvaptan, serum sodium declined to values similar to placebo[15].

Role of vaptans in CHF

Gheorghiade *et al* conducted a double-blind study investigating the effects of three doses of tolvaptan and placebo in patients with CHF[16]. 254 patients were randomly assigned to placebo (n = 63) or tolvaptan [30 mg (n = 64), 45 mg (n = 64), or 60 mg (n = 63)] once daily for 25 days. Patients were not fluid-restricted and were maintained on stable doses of furosemide. It was found in the study that in patients with CHF, tolvaptan was well tolerated; it reduced body weight and oedema and normalised serum sodium in the hyponatremic patients[16]. Another randomised, double-blind, placebo-controlled trial evaluating tolvaptan in CHF patients is the ACTIV in CHF trial. In this trial 3 oral doses of tolvaptan (30, 60 and 90 mg) were compared with placebo in 319 hospitalised subjects[17]. A significantly greater median reduction in body weight was observed in patients treated with tolvaptan when compared with those receiving placebo ($p \leq 0.009$). This effect was dose independent. Body weight further decreased in all groups during hospitalisation. Urine volume on day 1 was significantly higher for all tolvaptan groups. A total of 68 patients (21.3%) had mild hyponatraemia (serum sodium level < 136 mmol/l) at randomisation. These patients showed a rapid increase in serum sodium levels compared with placebo that was sustained throughout the study. Although there was no difference between the tolvaptan and placebo groups in the rate of worsening heart failure at 60 days, patients in the tolvaptan group required less diuretic than the placebo group in the out-patient setting. Tolvaptan did not appear to cause hypotension, tachycardia, worsening renal function, or hypokalaemia[17].

Role of vaptans in cirrhosis

Tolvaptan was found effective in raising serum sodium levels in patients with cirrhosis[14]. Conivaptan should be avoided in cirrhosis because it can increase the risk of variceal bleeding[18].

Other Vaptans

A. Lixivaptan

Wong *et al* conducted a study to investigate the efficacy and safety of 3 different doses of the V2 receptor antagonist lixivaptan. Forty-four hospitalised patients were included in this study out of them 33 were having cirrhosis. 6 were having CHF and 5 were having SIADH. They were randomised to receive 25, 125, and 250 mg twice daily of lixivaptan or placebo. It was found that lixivaptan produced a significant overall aquaretic response compared with placebo, with significant dose related increases in free water clearance ($p < .05$) and serum sodium ($p < .05$), without significant changes in orthostatic blood pressure or serum creatinine levels[19]. High dose was of lixivaptan, i.e., 250 mg twice daily experienced increased thirst and dehydration[19]. Gerbes *et al* investigated the effect of lixivaptan in patients with cirrhosis and dilutional hyponatraemia[20]. In this study, 60 patients with cirrhosis and dilutional hyponatraemia were randomly assigned to 100 or 200 mg/day of lixivaptan or placebo in a double-blind study. Treatment was given with fluid restriction (1,000 ml/day) until normalisation of serum sodium or for 7 days. Normalisation of serum sodium concentration was achieved in 27% and 50% of patients in the lixivaptan 100 mg/day and 200 mg/day groups, respectively, but in none of the patients in the placebo group ($p < 0.05$ and $p < 0.001$, respectively). Treatment with lixivaptan was associated with a significant reduction in urine osmolality and body weight. Thirst sensation increased significantly in the lixivaptan 200 mg group but not in the lixivaptan 100 mg or placebo group[20].

B. Satavaptan

Soupart *et al* investigated the effect of satavaptan in patients with SIADH[21]. In the first part of this multicenter trial, patients were randomly assigned to take either placebo or 25 mg or 50 mg daily of satavaptan for 5 - 23 days to obtain serum sodium within the range of 135 - 145 mmol/l. During the entire study, fluid intake was limited to 1,500 ml/day. Baseline serum sodium levels were 125 - 127 mmol/l in the three treatment groups. Responders, defined as achieving normal serum sodium or increasing serum sodium level by at least 5 mmol/l from baseline over at least a 24 hour period, were 79% (11 out of 14 patients) in the 25 mg group ($p = 0.005$ versus placebo), 83% (10 out of 12 patients) in the 50 mg group ($p = 0.005$ versus placebo) and 13% (1 out of 8 patients) in the placebo group. Urine osmolality decreased and free water clearance increased with satavaptan[21].

The long-term, open-label part of the study where 18 patients continued on satavaptan at doses 12.5, 25 and 50 mg once daily for a period of 12 months showed effectiveness of satavaptan in maintaining normal serum sodium without drug escape and adverse effects. Hypernatraemia developed in two patients during the double-blind period and five patients during the open-label period with satavaptan. No other drug-related serious events were reported.

Conclusion

Conventional treatment of hyponatraemia is unpredictable and troublesome. Recent studies have shown that vaptans are quite efficacious in treating hyponatraemia associated with SIADH, CHF, and cirrhosis. Vaptans are well tolerated with only minor side-effects including dry mouth, thirst, and polyuria. Osmotic demyelination syndrome associated with rapid correction of hyponatraemia has not been reported with the use of these agents till now. Presently, vaptans appear to be very effective in treating euvolaemic and hypervolaemic hyponatraemia, but further studies on a large number of patients are required to confirm the safety profile of these drugs.

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Osteoporosis: Physician's perspective

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Introduction

Osteoporosis is characterised by decreased bone strength with deterioration in skeletal microarchitecture leading to increased risk of fractures due to enhanced bone fragility. It is frequently prevalent in post-menopausal women, but also occurs in men and women with risk factors associated with bone demineralisation. Fracture can occur at any skeletal site, but vertebral, wrist, and hip fractures are the major clinical manifestations of osteoporosis[1]. Osteoporosis is generally a silent disease, reflected as low bone density measured by dual energy X-ray absorptiometry (DEXA scan) until a fracture occurs. The World Health Organization (WHO) defines osteoporosis as bone density that falls 2.5 standard deviation (SD) below the mean for young healthy adults of the same gender (also known as T-score of -2.5). Post-menopausal women having low bone density defined as subjects who fall at the lower end of young normal range of bone density (T-score of >1SD below the mean) are also at increased risk of osteoporosis. Osteoporosis occurs more frequently with increasing age as bone tissue is progressively lost after fourth decade of life. In women, loss of ovarian function at menopause precipitates a more rapid bone loss[2].

Pathophysiology

Bone remodelling is fundamental to the pathophysiology of osteoporosis. During growth, the bones increase in size by linear growth and by modelling, a process by which new bone tissue is apposed on the outer surface of the cortex. Increased sex hormone production at puberty is required for skeletal maturation, which reaches maximum bone mass and density in early adulthood. It is around puberty that the sexual dimorphism in skeletal size becomes obvious, although true bone density remains similar between sexes. Though genetic factors primarily determine peak bone mass and density, the nutrition and lifestyle also play an important role in growth. In adults, bone remodelling, and not modelling, is the principal metabolic process in the bones. Bone remodelling has two primary functions – to repair microdamage within the bone to maintain its strength and to supply calcium from skeleton to maintain serum calcium. Remodelling is activated by microdamage to the bones as a result of excessive stress. Acute demand of calcium involve osteoclast-mediated resorption and calcium transport by osteocytes. Chronic demands for calcium result in secondary hyperparathyroidism, increased bone remodelling, and loss of bone tissue[3].

Bone remodelling is also regulated by several circulating hormones including oestrogens, androgens, vitamin D, and parathyroid hormone, It is also regulated by locally produced growth factors such as IGF-I and II, transforming growth factor (TGF) beta, parathyroid-related peptide (PTHrP), interleukins (ILs), prostaglandins, and tumour necrosis factors (TNF). These factors primarily modulate the rate at which new remodelling sites are activated. The cytokine responsible for communication between osteoblasts, other marrow cells and osteoclasts has been identified as RANK ligand (receptor activator of NF-kappa-B). RANK ligand is a member of TNF family, and is secreted by osteoblasts and certain cells of immune system. The osteoclast receptor for this protein is referred to as RANK. The activation of RANK by RANK ligand is final common pathway in development and activation of osteoclasts. Osteoprotegerin, a humoral decoy of RANK ligand (also secreted by osteoblasts) also appears to play a role in modulation of osteoclast recruitment and activity along with RANK and RANK ligand[4,5]. Additional influences on bone remodelling include nutrition particularly calcium intake and physical activity level.

In young adults resorbed bone is replaced by an equal amount of new bone tissue. Thus, the mass of skeleton remains constant after peak bone mass is achieved in adulthood. After the age 30 - 45, the resorption and formation processes become imbalanced, the former exceeds the later. This imbalance may begin at different ages and varies at different skeletal sites; it becomes exaggerated in women after menopause. Peak bone mass may be impaired by inadequate calcium intake during growth period. During adult phase of life, inadequate calcium intake contributes to relative secondary hyperparathyroidism and increase in rate of remodelling to maintain normal serum calcium levels. Long-term effect of inadequate calcium intake are detrimental to skeleton because the increased

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remodelling rates and the ongoing imbalance between resorption and formation at remodelling site combine to accelerate loss of bone tissue. Total daily calcium intakes of less than 400 mg are detrimental to peak bone mass and intakes of 600 - 800 are also found to be suboptimal. Total daily calcium intakes of 1,000 - 1,200 mg have been recommended for adult population to keep the calcium metabolism in balance[6].

Vitamin D deficiency may be more prevalent, particularly among elderly, in individuals with poor nutrition, malabsorption, chronic liver disease, and chronic kidney disease. Vitamin D insufficiency leads to compensatory secondary hyperparathyroidism and is an important risk factor for osteoporosis and fractures. Treatment with vitamin D can bring serum 25-hydroxy vitamin D levels to optimal 30 ng/ml and prevent the associated increase in bone remodelling, bone loss, and fractures[7].

Oestrogen deficiency probably causes activation of new bone remodelling sites and exaggeration of imbalance between bone formation and resorption after the cessation of ovarian function at the time of menopause. Marrow cells and bone cells express oestrogen receptors (ERs). Loss of oestrogen increases production of RANK ligand and reduces the production of osteoprogerin increasing osteoclastic activity. Also, in an oestrogen deprived state, life span of osteoblasts may be decreased and longevity and activity of osteoclasts are increased. Since remodelling is initiated at the surface of the bone, the trabecular bone which forms almost 80% of total surface area will be preferencially affected by oestrogen deficiency. Therefore, the vertebral fractures are the most common early consequence of oestrogen deficiency[8].

Physical inactivity, such as prolonged bed rest, and paralysis result in significant weight loss. Athletes have higher bone mass as compared to general population because of their increased physical activity. Adults are less capable of increasing bone mass following good physical activity. Long-term high levels of physical activity have beneficial effects on skeletal strength and bone mass. It is presumed that more active individuals are less likely to fall and are more capable of protecting themselves upon falling and have low risk of fracture[9,10,11].

Fragility fractures

Fragility fractures are the fractures which occur with minimal or in-apparent trauma that might be insufficient to cause fracture in a normal healthy bone. Fall from standing height or less, like falls from bed are considered as fragility fractures. Most common site of fragility fractures are distal end of radius, vertebrae, neck of femur, and greater trochanter[12].

Classification

Osteoporosis can be classified as primary or secondary. About 80% cases of osteoporosis in men, and more than 95% in women are primary osteoporosis. Most cases of primary osteoporosis occur in older men and post-menopausal women. Gonadal insufficiency, inadequate calcium intake, low vitamin D levels are important contributing factors for primary osteoporosis. Secondary osteoporosis occurs more commonly in men than women. Multiple myeloma, chronic obstructive airway disease, chronic liver disease, chronic kidney disease, hyperparathyroidism, hyperthyroidism, hypogonadism, hyperprolactinaemia, diabetes mellitus, rheumatoid arthritis, hypervitaminosis A, and drugs (glucocorticoids, antiepileptic drugs, rosiglitazone, pioglitazone, thyroxine, heparin, alcohol, and tobacco) are the causes of secondary osteoporosis[12].

Risk factors

Human beings of all races and ethnicity are prone to osteoporosis and fracture. Blacks have greater and Asians have lower bone mass than whites. Several risk factors contribute to low bone mass. These include non-modifiable factors like female sex, old age, small thin built, Caucasian/Asian race and family history of fractures. Ethnic differences in bone mineral density (BMD) are strongly influenced by body weight. Low body mass index predisposes to decreased bone mass[13]. Important modifiable risk factors include calcium and vitamin D deficiency, sedentary lifestyle, smoking, excessive alcohol, and caffeine intake. History of fracture in relatives, weight < 60 kg, and height < 155 cm are significant risk factors for osteoporosis. Excessive caffeine intake and decreased agility increase the risk of hip fracture.

Drugs like glucocorticoids, antiepileptic drugs, glitazones, cytotoxic agents, heparin, aluminium, lithium, immunosuppressive drugs like cyclosporine and tacrolimus, aromatase inhibitors (anastrozole and letrozole used for breast cancer treatment), excessive alcohol, gonadotropin-releasing hormone agonists/antagonists (androgen deprivation therapy), and excessive doses of thyroid hormone accelerate bone remodelling and have a detrimental effect on bone density and risk of fracture.

Glucocorticoids are widely used drugs in the treatment of various diseases like chronic obstructive airway disease, asthma, nephritic and nephrotic syndrome, rheumatoid arthritis and other connective tissue disorders, inflammatory bowel disease, and post-transplantation of various organs. Osteoporosis and related fractures are serious side-effects of chronic glucocorticoid therapy. The

risk of fractures depends on the dose and duration of therapy. Bone loss is more rapid during the early months of treatment, and trabecular bone is more severely affected than cortical bones. Bone loss can occur with any route of steroid administration even with high dose inhaled glucocorticoids and intraarticular injections. Alternate day therapy does not appear to reduce the skeletal effects of glucocorticoids.

Clinical features

Osteoporosis is a silent disease and patients remain asymptomatic until a fracture has occurred. Vertebral compression fractures are usually asymptomatic in about 2/3 of the cases, while hip and wrist fractures are typically symptomatic. Symptomatic vertebral fracture begins with non-radiating acute onset pain aggravated by weight bearing accompanied by spinal tenderness. Pain of vertebral compression fracture typically subsides in 1 - 2 weeks. Multiple compression fractures of dorsal spine cause kyphosis with exaggerated cervical lordosis.

Diagnosis

Several non-invasive techniques such as dual energy X-ray absorptiometry, single energy X-ray absorptiometry, quantitative computerised tomography, and ultrasound are available for estimating bone mass or density. Dual energy X-ray absorptiometry (DEXA) is the gold standard for diagnosing osteoporosis by measuring bone density. Though it can be used for measurement of any skeletal site, clinical determinations are usually based on lumbar spine and hip. Hip is the preferred site for measurement of bone density in most individuals since it predicts the risk of hip fracture, the most important consequence of osteoporosis better than any other site. In DEXA technique, two X-ray energies are used to estimate the area of mineralised tissue, and the mineral content is divided by the area which partially corrects for body size. This correction is only partial since DEXA is a two dimensional scanning technique and cannot estimate the depth of the bone. Thus Indians, being small-sized, tend to have lower than average bone mineral density (BMD). Portable DEXA machines have been developed that measure the calcaneum, radius, ulna, and phalanges. DEXA results are reported as T-scores and Z-scores. The T-score is the standard deviation (SD) difference between the BMD of the patient and sex-matched young adult of reference population. The Z-score is the SD difference between the patient's BMD and an age, sex, and ethnicity matched population[13].

Computerised tomography (CT) is used primarily to visualise spine and hip. Peripheral CT is used to determine bones in forearm (radius and ulna) and tibia. CT being a three dimensional technique provides true density of bone tissue. CT can also specifically analyse trabecular bone and cortical bone content separately. However, CT involves greater radiation exposure, remains expensive and is less reproducible than DEXA.

Osteoporosis may be diagnosed in post-menopausal women and men $\geq$ 50 years of age when lowest T-score of lumbar spine, femoral neck, total hip or lower 1/3 of radius is –2.5 or less by World Health Organisation (WHO) criteria. The cut-off T –2.5 is selected because it identifies approximately 30% of post-menopausal women as having osteoporosis (by measurement of BMD at these sites), which approximates the life time risk of fracture at these sites. WHO diagnostic criteria for osteoporosis is used to classify bone mineral density in postmenopausal women and men aged 50 years or more. A T-score of –0.1 or above is taken as normal. Low bone mass or osteopenia is suggested by a T-score below –1.0 and above –2.5. T-score –2.5 or below indicates osteoporosis. Severe osteoporosis is indicated by personal history of fragility fracture with a T-score –2.5 or below. A presumptive diagnosis of may also be made in the presence of a fragility or low trauma fracture. WHO criteria is not applied in children, pre-menopausal women, and men under 50 years of age, and Z-scores (not T-scores) should be used[14].

Evaluation of patients with newly diagnosed osteoporosis

The evaluation of a patient with newly diagnosed osteoporosis should begin with a detailed medical history and physical examination. The history should include information about diet, lifestyle, asthma/chronic obstructive airway disease, diabetes mellitus, joint pain, malabsorption, seizure disorders, inflammatory bowel disease, hypothyroidism/hyperthyroidism, medication, family history of fall, and fractures. Clinical examination should include height, weight, tachycardia, tachypnoea, signs of hyperthyroidism, asthma, drug induced Cushing's disease, hypogonadism, signs of deep vein thrombosis (contraindication for treatment with oestrogen and raloxifene), signs of complications of osteoporosis like kyphosis, and loss of height, risk of fall like unsteady gait, and imbalance, paralysis and immobility joint laxity, blue sclera, hearing loss, poor dental development, osteoarthritis, inflammatory arthritis. Laboratory evaluation include complete blood count, measurement of serum calcium, magnesium, phosphorus, 25-hydroxy vitamin D, serum ALT/AST, serum alkaline phosphatase, (intact) PTH levels, TSH, 24 hours urinary calcium, creatinine and testosterone in men. X-ray imaging of spine for vertebral fracture, nuclear bone scan or X-ray for Paget's

disease should be carried out and taken into account for planning treatment for osteoporosis.

FRAX tool

Fracture risk assessment tool (FRAX tool) has been developed by WHO to estimate 10 years probability of hip fracture and major osteoporotic fracture in untreated men and women between 40 to 90 years of age. Age, sex, height, weight, ethnicity, femoral neck bone mineral density, history of previous fracture, parent with hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and consumption of 3 or more units of alcohol per day are the factors taken into account for calculating 10-year probability of major osteoporotic fracture[15]. The FRAX score provides the individual patient, in percentage terms, with an absolute risk of hip fracture or any osteoporotic fracture over the next 10 years, thereby allowing more informed decision making based on each patient's risk of fracture without active treatment. For example, in a 65-year-old woman with no fractures or other risk factors, but a bone mineral density T-score of – 2.5, the 10-year probability of a major fracture would be 13% and the 10-year probability of a hip fracture would be 2.8%. During a 3-year, randomised, controlled trial of a drug that would be predicted to reduce fractures by 40%, a total of 4.0% of subjects in a placebo group would sustain a fracture as compared with 2.4% of subjects in the treatment group. Providing these data to potential patients would inform decision making at all levels[15].

Management

All women aged 65 years or more, women younger than 65 years with 10-year probability of major osteoporotic fracture $\geq$ 9.3%, older males and men who are at increased risk of osteoporosis and are candidates of drug therapy should have a BMD test[16,17]. Guidelines suggest that patient should be considered for treatment when bone mass density is > 2.5 SD below the mean value for adults (T-score > -2.5). The treatment should also be considered in post menopausal women with risk factors like age, history of prior fracture, family history of hip fracture, low body weight, cigarette smoking, excessive alcohol consumption, steroid use, and rheumatoid arthritis, even if BMD is not in osteoporotic range. The goal of treatment is to reduce the risk for fractures. BMD should be measured 1 to 2 years after starting the therapy with the goal of maintaining or increasing the BMD.

Nutritional recommendations: Calcium and vitamin D are essential nutrients for growth of bone in childhood, and adolescence and maintenance of bone mass in adulthood. The optimum calcium intake reduces bone loss and suppresses bone turnover. The preferred source of calcium is from dairy products and other foods, but many patients require calcium supplementation. Dairy products such as milk, yogurt, and cheese are rich source of calcium. A daily calcium intake of at least 1,200 mg with diet plus supplements if needed for post-menopausal women and men aged $\geq$ 65 years, and for period of increased requirement like pubertal growth, pregnancy and lactation with maximum of 2,500 mg is recommended[18]. Excessive calcium intake is associated with increased risk of hypercalciuria and renal calculi. Achlorhydria affects absorption of calcium carbonate predominantly in the fasting state. In patients with achlorhyria or malabsorption, higher dose of calcium is required (up to 2,000 mg/day). Calcium carbonate is best taken with meals because of high prevalence of proton pump inhibitor-induced reduced gastric acidity. Calcium citrate can be taken with or without food because it is well absorbed regardless of gastric pH. Vitamin D has important effect on the uptake of calcium from the gut. Less than 50 - 100 mg of urinary calcium excretion inspite of adequate intake and normal kidney function suggests calcium malabsorption.

Normal blood level of 25-hydroxy vitamin D is necessary for normal bone health. The natural form of vitamin D (cholecalciferol) is synthesised in skin under the influence of ultraviolet light on 7-dehydrocholesterol. This naturally synthesised form is the major source of vitamin D for human body. However, the large urban Indian population does not synthesise sufficient quantity of vitamin D to maintain adequate supply. The natural dietary sources of vitamin D include egg yolk, fish, butter, and milk, but these contribute very little to the body's requirement. Cholecalciferol itself is not biologically active, and is converted in the liver to 25-hydroxycholecalciferol which is further hydroxylated to the active form 1,25-dihydroxycholecalciferol in the kidneys. Vitamin D supplementation at doses sufficient to achieve an adequate serum level of 25-hydroxy vitamin D (30 ng/ml) is safe and inexpensive. Thus daily intake of 200 IU of vitamin D for adults less than 50 yrs, and 800 to 1,000 IU for adults aged 50 years or more is recommended[19]. Vitamin D toxicity with hypercalcaemia is rare and is observed in patients taking a daily dose in excess of 40,000 IU[20]. Vitamin D should always be administered with calcium supplementation. Severe vitamin D deficiency should be treated with initially 60,000 IU weekly for 3 - 12 weeks followed by maintenance therapy. In case of intestinal malabsorption, vitamin D can be replenished with 2,50,000 IU intramuscular biannually. Patients with chronic kidney and liver disease should be supplemented with active form of vitamin D (1,25-dihydroxycholecalciferol). Urinary calcium excretion of >

250 mg/24 hrs predispose a patient to kidney stones and patient should be treated with reduced doses of vitamin D and calcium[20].

Lifestyle measures: Regular exercise in young individuals helps to attain the maximal genetically determined peak bone mass. Weight-bearing exercise improves bone strength by stimulating bone formation[11,21]. Exercise also has a beneficial effect on neuromuscular function, improves coordination, balance, and strength, thereby reducing the risk of falling. A regular walking programme is the most practical inexpensive way of exercise for all segments of population. Excessive heavy exercise may be harmful to bone health in adolescents and young adults with poor nutrition and hormonal abnormalities as seen in female athletes (eating disorder, amenorrhoea, and osteoporosis). Weight-bearing exercise, avoidance of smoking, moderation of alcohol consumption, and good nutrition are recommended for good bone health.

If possible, exposure to drugs (like glucocorticoids, aromatose inhibitors, LHRH agonist/antagonists, antiepileptics, etc.) known to have harmful effects on bones should be avoided. Prevention of falls in elderly patients by emphasising home safety, minimising use of sedatives, hypnotics, and narcotic analgesics that may cause sedation, hypotension, or giddiness, is of utmost importance.

Risk factor reduction: Preventive measures are advocated for post-menopausal women, older men, patients on long-term steroids, patients with osteoporosis, patients with osteopenia and multiple risk factors and secondary osteoporosis. The goals are directed to preserve the bone mass and to prevent the fractures. Risk factor reduction is the basic strategy in prevention and management of osteoporosis[12].

Pharmacological interventions: Pharmacotherapy is expensive and should therefore be targeted to those at high risk of fractures. Vitamin D deficiency-induced osteomalacia is very common. Therefore, all patients should undergo investigations for osteomalacia by getting serum levels of calcium, phosphorus, alkaline phosphatase, and (intact) PTH measured. Osteomalacia, if present, should be treated first. If vitamin D deficiency is a major contributor to the low bone density, very striking rises in bone density can be observed with calcium and vitamin D supplementation.

The American College of Physicians recommends pharmacologic treatment to men and women who are at risk of developing osteoporosis, have osteoporosis, and to those who have experienced fragility fractures[18]. In early post-menopausal years, oestrogen deficiency in women with low peak bone mass and BMD causes rapid bone loss due to accelerated bone remodelling. Therefore, early pharmacologic intervention in these conditions may prevent osteoporosis and ultimately reduce fracture risk[22,23]. Pharmacological agents proven to reduce fracture risk in patients with osteoporosis are classified into anti-catabolic drugs (bisphosphonates, raloxifene, oestrogen, and calcitonin) and anabolic agents (teriparatide) depending on their effects on bone remodelling and with respect to the mechanisms of fracture reduction. When deciding the treatment, aspects like individual values, absolute risk of fracture, extra-skeletal effects, and costs need to be considered. If the goal is to decrease risk of vertebral fractures, then the choices would include raloxifene or bisphosphonates in mild cases. Bisphosphonates (alendronate, risedronate, pamidronate, zoledronic acid, or ibandronate) are clearly the drugs of choice in the usual moderate to severe osteoporosis. If the goal is to reduce the risk of vertebral and non-vertebral fractures, then bisphosphonates would be the automatic choice, but for those with severe osteoporosis especially with pre-existing fracture, teriparatide would be the preferred option. The role of calcitonin has gradually declined with the availability of newer agents.

Bisphosphonates: Bisphosphonates are structurally related to pyrophosphates compounds that are incorporated into bone matrix. These are widely used drugs for treatment of osteoporosis and have a high affinity for bone and reduce bone resorption by causing loss of osteoclastic resorptive function as well as reduce osteoclast number by accelerating osteoclast apoptosis by inhibiting fernesyl pyrophosphate synthase, an enzyme in the HMG-CoA reductase pathway. In this group alendronate, risedronate, ibadronate, and zoledronate are the four drugs currently in clinical use. These drugs differ in their strength for binding to bone. The decreasing order for their binding affinity is zoledronate > alendronate > ibandronate > risedronate. High binding affinity bisphosphonates have very long retention in skeleton and exert long-term effects as these bind avidly to bone surface but spread through bone more slowly. Lower affinity agents are distributed more widely through the bone but have a shorter residence time in bone if treatment is stopped[24]. The oral bisphophonates alendronate, risedronate, and ibandronate are first line therapy for treatment of osteoporosis for many patients due to proven efficacy, safety profile, and low cost. Bisphospohnates preserve bone mass by inhibiting bone resorption and can decrease vertebral and hip fractures by 50%. Alendronate is given orally 10 mg once/day or 70 mg once in a week. Risedronate is given 5 mg once/day, 35 mg once in a week or 150 mg once in a month. Ibandronate can be given orally (150 mg once in a month) or intravenously (3 mg once in 3 months). Oral

bisphosphonate should be taken on an empty stomach with a glass of water (250 ml), without any food or other medications and patient should remain upright for at least 30 minutes (60 minutes in case of ibandronate) to reduce risk of oesophagitis. These drugs are contraindicated in patients with hypocalcaemia, kidney disease (creatinine clearance < 30 - 35 ml/min) or oesophageal stricture. These are used with precaution in patients with swallowing difficulty, severe gastro-oesophageal reflux disease, gastric bypass, or diseases treated with long-term anticoagulation. Patients with history of peptic ulcer disease and gastro-oesophageal reflux disease controlled with drugs can take oral bisphosphonates without difficulty. However, these drugs can be discontinued if symptoms of oesophagitis (retrosternal pain and worsening reflux symptoms) reappear. Injectable ibadronate or zolendronate can be used for treatment of osteoporosis when oral bisphosphonates are ineffective, contraindicated, associated with gastrointestinal intolerance, likely to be poorly absorbed, or if patient is not able to remain upright for 30 - 60 minutes after taking medicine[24].

Zoledronic acid is a potent bisphosphonate with high affinity for bone and has a unique once yearly intravenous administration regimen (5 mg single IV infusion over no less than 15 minutes every 12 months for treatment and every 24 months for prevention), approved for use for prevention and treatment of post-menopausal osteoporosis and glucocorticoid-induced osteoporosis in women and men. It has been found to be effective in fracture risk reduction. The common adverse drug reaction with intravenous bisphosphonates is a mild, transient flu-like illness. Intravenous bisphosphonates should not be given to patients with severely impaired kidney functions.

Bisphosphonate drug holiday: The skeletal binding site for bisphosphonates are virtually unsaturable and a substantial amount could be accumulated in the bones over time which continues to be released for months or years after the treatment is stopped. Therefore, it is reasonable to consider drug holiday from bisphosphonate therapy, a period of time when drug is stopped after continuous treatment and can be restarted after some time off[25]. In terms of long-term safety of bisphosphonate use, osteonecrosis of jaw (ONJ) and atypical femur fractures (AFF) are the two uncommon but important complications of bisphosphonates therapy[26,27]. Osteonecrosis of the jaw has been described in cancer patients treated with high doses of zoledronic acid or pamidronate. Invasive dental procedures, intravenous route of administration, and cancer are various risk factors for osteonecrosis of jaw. Atypical femur fractures occur in the mid-shaft of the femur with minimal or no trauma and may follow weeks or months of thigh pain. Because of these complications also drug holiday (stopping bisphosphonate) is recommended after 05 years of use of bisphosphonate therapy in patients with osteoporosis with few or no risk factors for bone loss and after 10 years of use in osteoporosis with more risk factors. Patients on a drug holiday should be monitored for a new fracture, accelerated bone loss and/or evidence of increased bone turnover, and if so, patients should be restarted on bisphosphonates or switched over to a different therapy. With bisphosphonates therapy bone turnover is suppressed for up to $\geq$ 02 years of drug holiday which is evident by low N-telopeptide cross links (< 40 nmol/l) or C-telopeptide cross links. An increase in levels of these markers indicates an increased risk of fracture and patient should be restarted on bone antiresorptive drugs[28].

Oestrogen: Until recently hormonal replacement therapy with oestrogen either alone or with progesterone used to be the primary therapy for prevention and treatment of osteoporosis. Oestrogens reduce bone turnover, prevent bone loss, and induce small increase in bone mass of the spine, hip, and total body. Oestrogen with or without medroxyprogesterone improves BMD and reduces the risk of fracture in post-menopausal women. However, it is not recommended for osteoporosis because of the risk of breast cancer[29].

Denosumab: A human immunoglobulin G_2 (IG_2) monoclonal antibody genetically engineered in Chinese hamster ovarian cells, Denosumab is a RANK ligand inhibitor. It decreases bone resorption by attenuating osteoclastic activity. It is indicated for treatment of post-menopausal women with osteoporosis at high risk for fracture. It increases bone mass and decreases vertebral, hip and non-vertebral fracture rates. Important side-effects include cellulitis, eczema, and flatulence. It is indicated for treatment of osteoporosis in post-menopausal women at high fracture risk[30].

Raloxifene: A selective oestrogen receptor modulator (SERM) raloxifene has suppressive effect on osteoclasts and bone resorption and antagonises the effect of oestrogen in uterine and breast tissues. It reduces vertebral fractures by 50%, but does not reduce hip fractures. It also reduces the risk of invasive breast cancer. Given in the dose of 60 mg/day, it has been associated with increased risk of thomboembolic events, vasomotor symptoms, and fatal stroke. It can be considered in early post-menopausal women who cannot take bisphosphonates, are at high risk for breast cancer, with no history of thromboembolic disease, low risk of stroke, low risk of hip fracture. It is not recommended for premenopausal women or women concurrently using

oestrogen replacement[31].

Calcitonin: Calcitonin reduces bone resorption by decreasing osteoclast activity. Intranasal salmon calcitonin can be used for treatment of osteoporosis in women who are at least 5 years post-menopausal are not able to take other drugs. It is administered as a nasal spray at a dose of 200 IU per day in alternating nostrils. Rhinitis and irritation of nasal mucosa are the main side-effects. However, it has not been shown to reduce fractures and is not considered first line therapy for osteoporosis[32].

Teriparatide: A synthetic recombinant parathyroid hormone, teriparatide (PTH 1 - 34) can be used for treatment of patients having a history of osteoporotic fracture, multiple risk factors for fracture, intolerance to other antiresoptive drugs, and failure to respond to other antiresorptive drugs. It is the only osteoanabolic PTH analogue approved for use in post-menopausal osteoporosis, primary or hypogonadal osteoporosis in men, and patients with sustained systemic glucocrticoid therapy. It is given subcutaneously at a dose of 20 µg once daily for 18 - 24 months. It increases the bone mass, decreases vertebral and non-vertebral fractures. Dizziness and nausea are the common side-effects of triparatide[33]. It is contraindicated in patients with Paget's disease of bone and risk of osteosarcoma.

Monitoring therapy

Serial BMD measurements by DEXA are recommended to be used to assess response to therapy. BMD can be measured every 12 or 24 months after initiating or changing the therapy. More frequent testing (every six months) is recommended in conditions with more rapid bone loss such as diseases mandating the use of glucocorticoid therapy[34].

Conclusion

Osteoporosis is a progressive metabolic bone disease characterised by compromised bone strength and low bone mass with enhanced bone fragility, and increased susceptibility to fracture. DEXA scan is the gold standard diagnostic test for osteoporosis. There is widespread vitamin D deficiency across the world including India, particularly in the urban Indian population. Poor sunlight exposure, sedentary lifestyle, and a vitamin D deficient diet are some obvious causes of vitamin D deficiency. Osteoporosis is a common disease with serious clinical outcome. A healthy lifestyle like balanced diet, daily exercise and adequate sunlight exposure can have a major positive impact on bone health and osteoporosis. People should be encouraged to carry out optimum daily outdoor physical activity, give up smoking, and limit alcohol consumption. All segments of population should receive an adequate calcium and vitamin D intake from the diet or from supplements. Indiscriminate use of steroids needs to be discouraged. Pharmacological interventions should be targeted to only those who have history of fractures or are at high risk of fractures. Bisphosphonates are the mainstay of therapy in the management of osteoporosis.

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"Early to bed and early to rise,
makes a man healthy, wealthy and wise."

– BENJAMIN FRANKLIN.

UPDATE ARTICLE

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Lower lung field pulmonary tuberculosis: An overview

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Introduction

Tuberculosis (TB) is one of the oldest diseases known to mankind. It is a major cause of morbidity and mortality all over the world including India. About one-third of the global population has been infected with *Mycobacterium tuberculosis* and it is estimated that prevalence of infection is about 40% in Indian population. With the highest burden of tuberculosis in the world, India has over two million incident cases amounting to more than a fifth of the global burden. As per the WHO Global TB Report 2011, there were an estimated 8.8 million incident cases of TB (range, 8.5 million - 9.2 million) globally in 2010, 1.1 million deaths (range, 0.9 million - 1.2 million) among HIV-negative cases of TB and additional 0.35 million deaths (range, 0.32 million - 0.39 million) among people who were HIV positive. In 2011, out of the estimated global annual incidence of about 9 million TB cases, 2.3 million were estimated to have occurred in India[1].

Table I: WHO estimated burden of tuberculosis in India, 2011.

	Number (millions) (95%CI)	Rate per 1,00,000 persons (95%CI)
Incidence	203 (2.0 - 2.5)	185 (167 - 205)
Prevalence	3.1 (2.0 - 4.6)	256 (161 - 373)
Mortality	0.32 (0.21 - 0.47)	26 (17 - 39)
	Number (Millions) (95%CI)	Percent (95%CI)
HIV among estimated incident TB patients	0.11 (0.075 - 0.16)	5% (3.3 - 7.1%)
MDR-TB among notified pulmonary TB patients	0.064 (0.044 - 0.075)	5.3% (3.6 - 6.2%)
Notified new pulmonary TB patients	0.021 (0.015 - 0.027)	2.1% (1.5 - 2.7%)
Notified re-treatment pulmonary TB patients	0.043 (0.039 - 0.048)	15% (913 - 17%)

Lungs are the most commonly involved site for tuberculosis and other organs are involved in about one-third cases. The common form of tuberculosis in adults is secondary tuberculosis or post-primary disease which is due to reactivation of latent infection. The commonest site of adult pulmonary tuberculosis is the apical and posterior segment of upper lobes because of higher mean oxygen tension which favours growth of mycobacteria. Superior segments of lower lobes are also frequently involved in adult tuberculosis. Post-primary tuberculosis has been classically considered as a disease causing patchy opacity or with cavitary or calcified lesion, in one or both upper lung lobes.

Many of us clinicians have an impression that tuberculosis affects only the upper lobe of lungs, which is true up to some extent because in about 90% cases of tuberculosis only the upper lobes of lung are involved. However, it is not uncommon to see patients presenting with history of about 2 - 4 weeks fever, dry or productive cough, and lower lung field consolidation on chest radiography. These patients do not respond to standard optimum antibiotic therapy for pneumonia and ultimately diagnosed as case of lower lung field pulmonary tuberculosis. In one study from Japan by Miyazaki *et al,* the incidence of lower lung field TB was 8.5% (57/672) and the average duration for diagnosis of lower lung field TB in patients over 65 years of age, was 71.7 days[2]. Another study from Iran where records of 146 patients of lower lung field TB were reviewed showed that average duration of symptoms before diagnosis was less than one month only in 7%, between 1 - 6 months in 63%, and more than 12 months in 10% cases[3]. Thus, it is evident that the diagnosis and treatment of tuberculosis is often delayed in these patients with lower lung field TB.

The awareness of involvement of lower lung field in pulmonary TB in the elderly, diabetes patients, immune-compromised persons, and pregnant women is important because delay in interpretation of these images might delay timely diagnosis and treatment of tuberculosis. The major impact on incidence of TB in India will be achieved by reducing diagnostic delays particularly if done in combination with deployment of high sensitivity initial diagnostic testing and improved overall cure rates. The aim of this article is to emphasise on the not so infrequent occurrence of lower lung field pulmonary tuberculosis so that the diagnosis and initiation of anti-tuberculosis therapy may not get unnecessarily delayed due to lack of

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adequate awareness amongst clinicians.

Lower lung field TB is usually primary pulmonary tuberculosis that occurs soon after initial infection with tubercle bacilli. In areas of high tuberculosis transmission, this form of tuberculosis is often seen in children and in persons with impaired immunity. Primary pulmonary tuberculosis may progress to clinical illness presenting as non-resolving pneumonia. In severe cases, the primary lesion enlarges rapidly and its central portion undergoes necrosis followed by formation of cavity. This form of pulmonary disease is known as primary pulmonary tuberculosis. Tuberculosis in young children is almost invariably accompanied by hilar or mediastinal lymphadenopathy due to spread of bacilli from lung parenchyma through lymphatic vessels. Haematogenous dissemination which is more common and often asymptomatic may result in more severe manifestations of primary tubercular infection. Bacilli gain access to blood stream from pulmonary region or lymph nodes and disseminate into various organs, where they may produce granulomatous lesions. Although in persons with normal immunity healing frequently takes place, immuno-compromised persons may develop military tuberculosis and/or tuberculous meningitis.

Definition

The lower lung field is the area of the postero-anterior chest radiograph extending below an imaginary horizontal line traced across the hila including parahilar regions. Lower lung field TB is defined as tuberculous involvement of lower lung fields without simultaneous involvement of upper lobe. Lower lung field includes right middle lobe, lingula, and lower lobes. Middle and lower lung zones are most commonly involved by primary pulmonary tuberculosis because most inspired air is distributed in the middle and lower lobes of lung. Lower lung field pulmonary tuberculosis is more common in children and in adults with impaired immunity when primary pulmonary tuberculosis progresses to clinical disease. It is seen more commonly in the elderly, persons with malnutrition, diabetes mellitus, chronic liver disease, chronic kidney disease, alcoholism, HIV infection, and patients receiving corticosteroids and/or other immunosuppressive drug therapy. Lower lung field tuberculosis often masquerades as non-resolving pneumonia which leads to delay in the diagnosis.

Epidemiology of lower lung field TB

Prevalence of lower lung field TB in India has been reported to be higher than in Western countries. In one Indian study Ahmed *et al*, observed highest incidence of lower lung field TB in 21 - 40 years age group patients. Mean age of male patients, having lower lung field TB was higher (35 yrs) than female patients (23 yrs). It was more common in females (12.1%) than in males (9.36%)[4]. In another study, lower lung field TB represented 6% of the pulmonary TB cases. No significant differences were found with respect to age, sex, the presence of cavities in chest X-rays, and days of evolution. Lower lung field TB had a significantly greater proportion of co-morbidity ($p < 0.001$), the presence of consolidation ($p < 0.001$), and unilateral involvement of lung ($p < 0.001$), with a higher number of hospital admissions ($p = 0.02$). However, only 38% (16/42) patients with lower lung field TB had a notable co-morbidity implying that lower lung field TB can be present without associated co-morbidities. It concluded that lower lung field TB must be suspected in pneumonias that have a slow evolution regardless of pulmonary localisation[5]. J Ayatollahi from Iran studied 217 patients having pulmonary TB and observed that incidence of lower lung field TB was 19.8% and majority of patients were above 60 years of age. It was more common in females (21.8%) than in male (17.7%) patients[6]. Chandrasekhara *et al,* analysed the clinical features of 40 cases of lower lung field TB. Various risk factors noted in this study were diabetes 35% (14/40), elderly 30% (12/40), alcoholics 17.5% (7/40), previous h/o pulmonary TB 10% (4/40), and HIV-infection 5%(2/40)[7].

Diabetes mellitus and lower lung field TB

Diabetes has long been known to be a risk factor for active tuberculosis and reactivation of latent tuberculosis. Worldwide, the International Diabetes Federation (IDF) predicted that the number of people with diabetes will rise by 55% in the next 20 years. An estimated increase in diabetes prevalence to 13% could reduce the fall in tuberculosis incidence by 8% or more. Increase in diabetes prevalence in India seems to have contributed to the absence of a decrease in tuberculosis incidence between 1998 and 2008, despite improvement in tuberculosis treatment[8].

India is experiencing an epidemic of diabetes with an estimated 80 million diabetics by the year 2030. The link between tuberculosis and diabetes mellitus (DM) has occupied the centre stage of discussion. Experts have raised concern about the merging epidemics of tuberculosis and diabetes particularly in the low to medium income countries like India and China that have the highest burden of TB in the world, and are experiencing the fastest increase in the prevalence of DM. There is good evidence that DM makes a substantial contribution to TB incidence. The huge prevalence of DM

in India, may be contributing to the increasing prevalence of TB. Diabetes accounts for 14.8% all tuberculosis and 20.8% all smear positive tuberculosis[9]. Diabetes has also been reported to modify the presenting features of pulmonary TB. There are varying data regarding the association of diabetes mellitus with lower lung field involvement in pulmonary TB. A higher frequency of lower lung field TB was described among pulmonary TB patients with diabetes mellitus. Ahmed *et al*, had observed higher rate of lower lung field TB in diabetics (18.49%) than in non-diabetics (9.62%)[4]. Bacackoglu *et al*, from Turkey compared the patients with tuberculosis and diabetes seen during one year period with an age- and sex-matched non-diabetic control group with tuberculosis. Duration of symptoms, tuberculin reaction, bacteriologic and radiographic findings of both the groups was compared. It was observed that diabetes did not have an effect on patients' symptomatology, sputum positivity, tuberculin reaction, and localisation of pulmonary infiltrates. Fewer diabetics were sputum smear positive and fewer had reticulonodular opacities compared with control patients. A higher number of insulin dependent diabetic patients presented with cavitary lesions compared with non-diabetic controls. Lower lung field TB was significantly associated with female gender and was more frequently observed with diabetes in patients older than 40 years. This study concluded that diabetes affects the presenting features of pulmonary tuberculosis to a large extent and is only associated with lower lung field disease in older patients[10]. Patel *et al*, studied 50 patients with pulmonary tuberculosis having diabetes and found that in diabetic patients there was higher involvement of lower lung field (84%) as compared to upper lung field (16%). Bilateral involvement was present in 32% while unilateral involvement was present in 68%. Ten out of 50 patients had cavitary disease. Cavitary lesions were more frequently confined to lower lung fields (80%). Nodular lesions were found in 36%, exudative lesions were found in 22% and mixed lesions were found in 22%. This study also supported that tuberculosis tend to be predominantly at lower lung fields in patients with diabetes. It concluded that the patients with tuberculosis and diabetes are more likely to present with atypical radiological features. In diabetes patients presenting with lower lung field lesions on chest radiograph, possibility of tuberculosis should always be considered for prompt diagnosis and management[11]. Qazi *et al*, from Pakistan studied chest radiographs of 150 patients of pulmonary TB with diabetes and observed that 69 (46%) films showed the typical pattern involving upper zone, while 81 (54%) films showed the atypical pattern with lower lung field involvement[12].

Pulmonary tuberculosis may occur more often among patients with diabetes mellitus than those without it. Diabetic patients have high incidence of lower lung field TB than in non-diabetic patients. Fever, cough and loss of weight are the most common presenting symptoms. Lower lung field involvement with non-homogenous opacities and cavitary lesions are common findings.

HIV infection and lower lung field TB

According to a report there were 1·8 million incident cases and 29.2 million prevalent cases of HIV infection, and 1.3 million HIV deaths reported in 2013 all over the world[13]. Higher incidence of TB has been reported in HIV-infected patients than in non-HIV-infected persons. HIV associated immune-suppression increases the risk of tuberculous disease either from reactivation or from progression of the primary infection. HIV-infected individuals are at higher risk of recurrence of pulmonary TB from exogenous infection. HIV co-infection accelerates course of pulmonary TB. However, HIV co-infection diminishes the infectiousness of pulmonary TB. While the HIV epidemic in India appears to have peaked, the total number of persons living with HIV/AIDS remains high, and with time the level of immune deficiency and TB vulnerability may increase. Patel *et al*, observed a higher involvement of lower lung field (41.86%) as compared to upper lung field (23.26%) in pulmonary tuberculosis patients with HIV co-infection, while 34.88% patients had extensive disease involving both upper and lower lung fields. Cavitary lesions were more frequently observed in extensive diseases (60%)[14]. Ahmed *et al*, observed significantly higher incidence of pulmonary tuberculosis in HIV-infected persons than in non-HIV-infected persons. Forty two (46.15%) out of 91 HIV-infected patients of pulmonary TB had lower lung field TB. Incidence of mediastinal lymphadenopathy and pleural effusion was equal in upper lung field TB, while in lower lung field TB incidence of mediastinal lymphadenopathy was higher as compare to pleural effusion. It concluded that in HIV positive patients, pulmonary tuberculosis is more likely to present with atypical radiological images[4].

Pulmonary tuberculosis may occur more often among patients with HIV infection than those without it. HIV-infected patients have high incidence of lower lung field TB than in non-HIV-infected persons. Therefore, we must consider pulmonary TB in all patients with atypical radiological presentations for early diagnosis and management of this disease in HIV-infected patients. Possibility of TB should always be considered in HIV-infected patients presenting with lower lung field involvement even without cavitary lesion.

Elderly persons and lower lung field TB

The common presentation of pulmonary TB in the elderly is based upon reactivation of old lesions. Typical sites involved are apical segments of both upper and lower lobes and the posterior segments of upper lobes. The disease may develop as pneumonia with caseation, liquefaction, and cavity formation. On the other hand, clinical picture of primary tubercular infection is different. Besides constitutional symptoms and cough, the chest radiographic abnormalities are seen in mid- and lower-zones. Due to this atypical presentation, the diagnosis may be missed unless a high index of suspicion is maintained and sputum or bronchial aspirate is subjected to smear and culture examination. Furthermore, little published data are available on HIV and tuberculosis co-infection in elderly. The diagnosis of HIV infection is also often missed in elderly because of less suspicion in them. Therefore, tuberculosis should be included in differential diagnosis of any illness in an elderly patient, which consists of ill defined pleura-pulmonary symptoms or signs and pulmonary infiltrates or cavitary lesion of unknown cause.

Pregnancy and lower lung field TB

Lower lung field TB as such has been found to have an association with female gender. Atypical presentation of TB in pregnant women often poses difficulties in confirming the diagnosis of tuberculosis. Many a times pregnant women remain asymptomatic and TB may be diagnosed incidentally or during screening. Some of the symptoms related to TB such as increased respiratory rate and fatigue, may mimic physiological changes occurring during pregnancy and thus, cause delay in diagnosis. Currently, it is believed that pregnancy neither predisposes to development of TB nor affects the progression of disease. However, it is not uncommon to see the involvement of lower lung fields in pulmonary tuberculosis during pregnancy.

Lower lung field TB versus upper lobe TB

Yoon *et al*, from Republic of Korea in a retrospective study compared clinical features and computed tomography finding of pulmonary TB in lower lobe basal segments and upper lobe apical or apico-posterior segments in 986 adults diagnosed with active pulmonary tuberculosis. Active pulmonary TB confined to the basal segments was found in 21 patients, whereas, 60 patients had disease localised to apical or apico-posterior segments only. Clinical features and CT abnormalties of lung parenchyma, airways, mediastinal and hilar lymph nodes, and pleura were compared between these two groups. Chest CT findings, including consolidation, lymphadenopathy, and pleural effusion were more common in basal segment TB than in apical or apico-posterior segment TB. Small nodules were less common in basal segment TB than in apical or apico-posterior segment TB. The tree-in-bud sign was most common CT finding in both basal segment (17/21, 81%) and apical or apico-posterior segment TB groups (53/60, 88.3%) (p = 0.4663). This study concluded that lower lobe basal segment TB was more commonly present with common finding of primary pulmonary TB including consolidation, mediastinal and hilar lymphadenopathy, and pleural effusion than apical or apico-posterior segment TB[15]. In another study conducted in Taiwan to compare the manifestations of lower-lung-field TB and other pulmonary TB, 79 new culture-proven TB patients with lower-lung-field consolidation were compared with age- and sex-matched TB patients with upper lung involvement. The clinical, radiographic and laboratory findings were similar in the lower lung field TB and the upper lobe TB groups, except that the lower lung field TB patients had less cavitation (P = 0.005). Patients with lower lung field TB were diagnosed (P = 0.051) and treated (P = 0.001) later. It was observed that calibres of the trachea and both main bronchi were significantly smaller in the lower lung field TB group (P < 0.001). More patients with lower lung field TB developed segmental or lobar atelectasis during follow-up (P = 0.028). In this study it was concluded that the manifestations of lower lung field TB are non-specific. The lower-lung involvement, the lower incidence of cavitation and the higher probability of segmental or lobar atelectasis implied that lower lung field TB was primary TB and a small bronchial calibre probably contributed to its development[16].

Lower lung field TB versus lower lung field pneumonia

The radiological manifestations of lower lung field TB being similar to those of lower lung field pneumonia (LLFP), makes diagnosis challenging. In one study conducted in Taiwan on 22 patients diagnosed with lower lung field TB and 72 patients diagnosed with LLFP revealed that age (odds ratio [OR] = 1.05, 95% confidence interval [CI] = 0.99 - 1.11, P = 0.072), lack of fever > 38°C (OR = 9.04, 95% CI = 1.69 - 48.40, P = 0.001), duration of symptoms ≥ 7 days (OR = 4.57, 95% CI = 1.09 - 19.26, P = 0.038), and the lack of air bronchograms on radiography (OR = 12.08, 95% CI = 1.98 - 73.64, P = 0.007) were significant predictors of lower lung field TB in patients with lower lung field opacities. The study suggested that older age, prolonged duration of symptoms, lack of fever > 38°C, and the absence of air bronchograms, are more common in patients with lower lung field TB than in patients with pneumonia. These findings may help clinicians

differentiate between lower lung field TB and lower lung field pneumonia and thus initiate timely and appropriate treatment[17].

Pathogenesis

Tuberculosis is an airborne infectious disease caused by an aerobic, non-motile, non-spore forming bacilli *Mycobacterium tuberculosis*. This organism is highly resistant to drying, acid, and alcohol. It is transmitted from a person with infectious pulmonary TB to others by droplet nuclei, which are aerosolised by coughing, sneezing, or speaking. These tiny droplets dry rapidly and may remain suspended in the air for several hours and may reach the terminal air passage when inhaled. There may be as many as 3,000 infectious nuclei expectorated per cough. Because of delays in seeking care and in making a diagnosis, it is estimated that, in high prevalence settings, up to 20 contacts may be infected by each sputum positive TB patient before he gets diagnosed and initiated on anti-tuberculosis therapy. The most common mechanism for pathogenesis of lower zone tuberculosis is ulceration of a bronchus, by a lymph node involved by tuberculosis, with tuberculous material spilling in to the bronchus. Lower lung field TB is thought to be a progressive primary disease or early post primary disease.

Clinical features

In most of the patients, duration of presenting symptoms in lower lung field tuberculosis is about two weeks with a mean duration of twelve weeks. Cough with or without expectoration is the most common presenting symptom followed by haemoptysis in about 2/3 cases of lower lung field tuberculosis. The general constitutional symptoms like fever, chills, malaise, weakness, anorexia, and weight loss are also frequently seen.

Physical signs are encountered more often in patients with lower lung field tuberculosis than in patients with typical upper lobe pulmonary tuberculosis. They may vary with the extent and character of the lesions and may be scanty or absent in patients with involvement of a small area of lung particularly where the lesion is limited to apical segment of lower lobe. Patients with extensive involvement of lower lung fields may have obvious signs of the underlying consolidation or cavity.

Diagnosis

The prompt diagnosis of TB is essential for community health infection control measures as well as ensuring optimum therapy for patients. Unfortunately, acid-fast bacilli are found in a limited number of patients with active pulmonary TB and therefore imaging modalities are of paramount importance in making a diagnosis of TB before definitive bacteriological diagnosis.

Sputum examination

As in upper lobe pulmonary tuberculosis, positive microscopic sputum examination for *Mycobacterium tuberculosis* is the simplest way to diagnosis lower lung field pulmonary tuberculosis. The diagnostic yield of sputum examination is better in patients with cavitary lesions in both upper lobe and lower lung field pulmonary TB. HIV related lower lung field TB is frequently associated with negative sputum smear due to low bacillary load. Sputum culture and sensitivity for *Mycobacterium tuberculosis* is required in smear negative patients and also to detect and treat drug resistance tuberculous infection.

Chest radiography

More than half of the cases of lower lung field TB have involvement of right lung (Fig. 1), whereas, almost 1/3 patients have involvement of the left lung (Fig. 2). Bilateral lung lesions are reported in about 10% cases of lower lung field tuberculosis (Fig. 3). Radiographic features in lower lung field tuberculosis are significantly different than those found in upper lobe pulmonary tuberculosis. Confluent and extensive consolidation is the most common radiographic finding in lower lung field TB; however, single or multiple cavitary lesions are also frequently seen amidst the area of consolidation. The presence of thin-walled fluid filled cavity (tension cavity), atelectasis, and solitary mass with mediastinal lymphadenopathy are also radiological features seen in lower lung field TB[18].

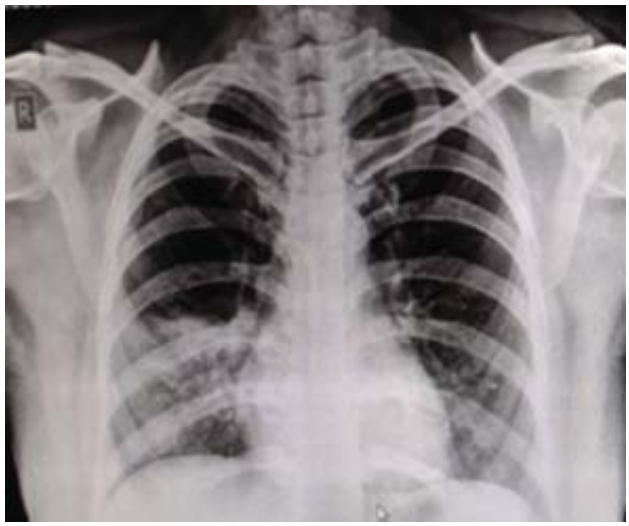

Fig. 1: *Chest radiograph - PA view showing right lower lung field tuberculosis in a 32-years female.*

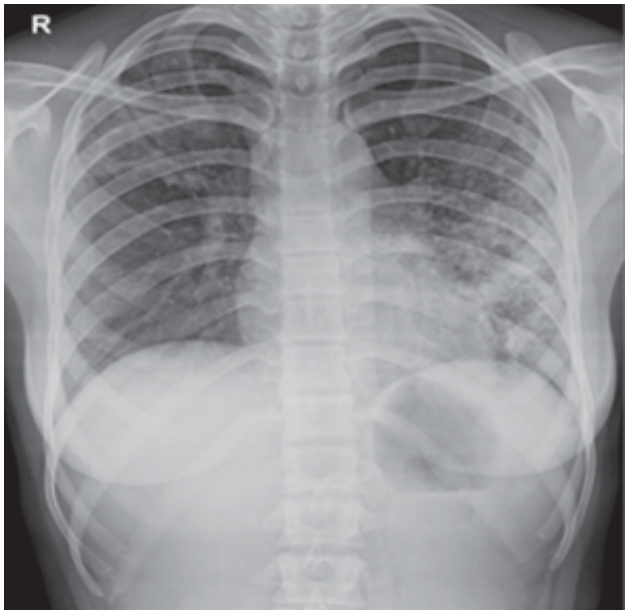

Fig. 2: *Chest radiograph - PA view showing left lower lung field tuberculosis presenting as left lower lobe consolidation in a 24-years female.*

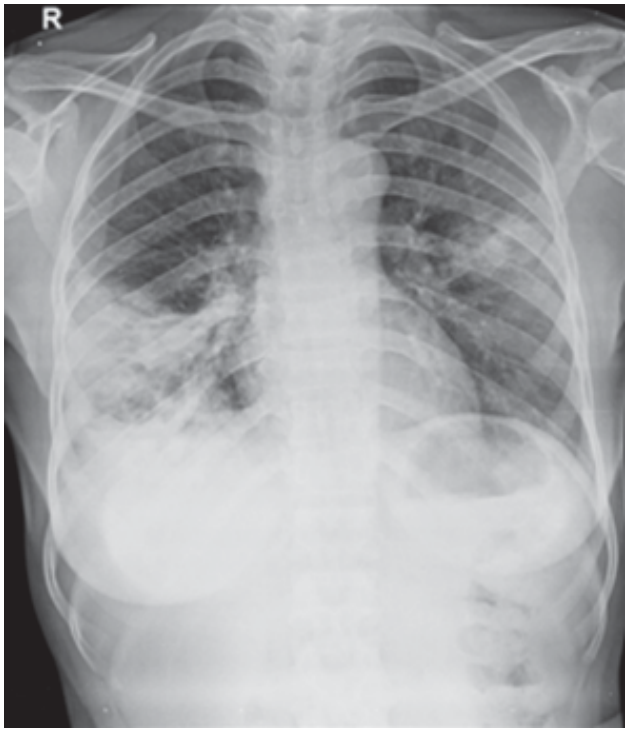

Fig. 3: *Chest radiograph - PA view showing bilateral lower lung field tuberculosis in a 42-years female.*

Computed tomography

Computed tomography (CT) can give important information in a patient with pulmonary TB and may identify foci in the lungs undetected by chest radiography. Occult cavity may be detected when obscured by pleural effusion, bone, or diaphragm. Bronchial stenosis or obstruction and nature and extent of bronchiectesis can be detected by CT. Mediastinal lymphadenopathy can be detected and nature of lymph nodes can be detected by CT. Miliary lesions can be detected by high resolution CT (HRCT) even when chest radiograph is normal. Therefore, CT has a definite role in symptomatic Mantoux positive patients with normal chest X-ray. CT findings of lower lung field pulmonary tuberculosis have not been widely investigated. Common CT findings in lower lung field TB are that of primary pulmonary tuberculosis and include consolidation, mediastinal and hilar lymphadenopathy, and pleural effusion. Consolidation is the most common finding in basal segment pulmonary TB[15]. However, sometimes cavitary lesions may be detected in lower lung field tuberculosis in elderly diabetic patients with chest radiograph showing only consolidation (Fig. 4).

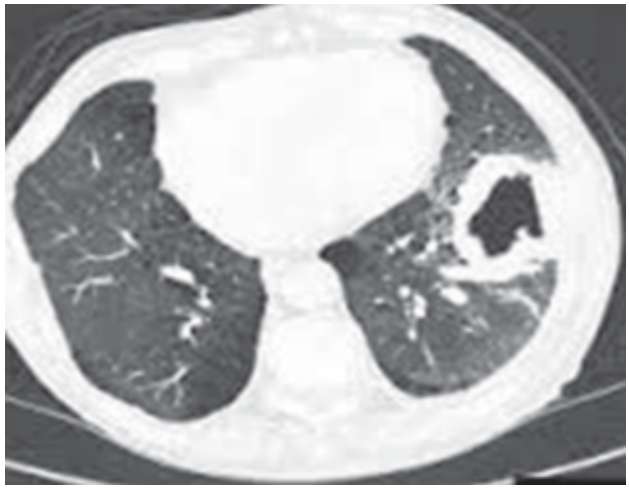

Fig. 4: *CT chest showing cavitary lesions in left lower lung field in a 72-years diabetic male.*

Bronchoscopy

Fibreoptic bronchoscopy (FOB) is the preferred diagnostic modality for chest clinicians for diagnosis of lower lung field tuberculosis. It provides a higher diagnostic yield than sputum examination, particularly in patients with pulmonary consolidation, collapse, or solitary mass. It is also important in assessing the severity of endobronchial lesions in lower lung field tuberculosis. Bronchoscopic findings in lower lung field tuberculosis include ulcerative granuloma, mucosal erythema, submucosal infiltration, and fibrostenosis. The outcome is unfavourable in patients with fibrostenosis and ulcerative granuloma. Surgical intervention should be considered in severe fibrostenosis to prevent damage of the lung parenchyma distal to obstruction[19].

Conclusion

Pulmonary tuberculosis is a disease with protean manifestations and can mimic many diseases. Lower lung field tuberculosis is not uncommonly seen in day-to-day clinical practice, and often masquerades as lower lobe pneumonia leading to unwarranted delay in diagnosis and treatment of patients with lower lung field TB. Elderly persons, diabetics, pregnant women, and immuno-compromised persons because of HIV infection and/or any other co-morbid conditions, are more likely to develop lower lung field TB. Older age, prolonged duration of symptoms, lack of moderate-to-high fever (> 38°C), absence of air bronchograms on chest X-ray, and non-resolution of pneumonia with optimum antibiotic therapy, are common indicators of lower lung field TB in patients with lower lung field opacities. Computed tomography has an important role in early diagnosis of lower lung field TB. These clinical and radiological findings may help clinicians in diagnosing and initiating timely and appropriate treatment of lower lung field TB.

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"The secret of enjoying life is to take an interest in it."

– THOMAS TROWARD.

CASE REPORT

JIACM 2015; 16(1): 67-9

Intradural extra-medullary arachnoid cyst presenting as paraparesis

P Agrawal, AK Singh*, S Sompura**, A Raj**

Abstract

The symptoms of spinal arachnoid cysts are variable and nonspecific, so they are commonly misdiagnosed. Often the cysts are discovered incidentally on magnetic resonance imaging (MRI). If they cause no symptoms, no treatment is warranted regardless of the size of the cyst. Cysts that cause symptoms from mechanical compression of the spinal cord are best evaluated with MRI and surgically excised if possible. A 20-year-old male presented to our clinic with chronic cervico-thoracic back pain and spastic paraparesis . MRI scan revealed evidence of intradural, extra-medullary arachnoid cyst at C7 – T5, compressing the cord. The patient was referred to dept of neurosurgery for surgical removal of arachnoid cyst.

Keywords: Arachnoid cyst, spastic paraparesis, magnetic resonance imaging.

Introduction

A patient with a clinically relevant spinal arachnoid cyst is most likely to be a boy in his teens, but these cysts can occur in either sex and have been reported in patients as young as a few months and as old as nearly 80 years[1-6]. In their typical presentation, spinal arachnoid cysts cause progressive signs and symptoms suggesting spinal cord compression. But because a cyst can occur at any spinal level and in a patient of any age, no one clinical presentation is pathognomonic. Nevertheless, we can make certain generalisations: a spinal arachnoid cyst that compresses the spinal cord typically causes waxing and waning pain and progressive spastic or flaccid paraparesis, which often are exacerbated by valsalva maneuvers[1,6]. Spinal arachnoid cysts can also present with symptoms suggestive of an isolated radiculopathy. Like other types of spinal meningeal cysts, spinal arachnoid cysts can be broadly characterised as either extradural or intradural[9].

Extra-dural cysts are extra-dural out-pouchings of arachnoid that are contiguous with the spinal subarachnoid space via a small dural defect. They typically occur in the thoracic spine dorsal to the spinal cord.

Intra-dural cysts are outpouchings of arachnoid that, regardless of size, lie entirely within the dural space. Intradural arachnoid cysts are more common than extra-dural cysts.

How spinal arachnoid cysts start to form is open to conjecture, and several theories exist[1,2,7]. They are often attributed to congenital defects. Another possibility is that arachnoid adhesions develop secondary to inflammation, which may arise from infection (meningitis), haemorrhage, or an iatrogenic cause such as injected contrast media or anaesthetics, or from the intra-operative contaminants of fibrin glue[10]. Some cysts are due to trauma from lumbar puncture, anaesthetic procedures, or intradural surgery. Other cysts are idiopathic.

Case report

A 20-year-old male presented with a history of chronic thoraco-lumbar back pain, and a progressive and bilateral lower limb weakness since birth. This was associated with spasms affecting his legs and abnormal sensation on the soles of the feet. He was asymptomatic in the upper limbs. On examination, there was spastic paraparesis, with an up-going plantar response on both sides, and exaggerated knee and ankle jerks. There was bilateral weakness (lower limb power 1/5 proximally and 0/5 distally). Sensory level with hypoaesthesia to light touch, pinprick, loss of vibration sense upto T1 level was seen. Cranial nerves and upper limbs were neurologically intact. There was no difficulty in defaecation and urination. Serum electrolytes were within normal range. A MRI scan of the spine revealed an intradural extra-medullary lesion extending from C7 to T4 - 5 level with signal characteristics equal to CSF with gross compromise of cord – probably arachnoid cyst (Fig. 1-2). Patient was referred to neurosurgery for surgical removal of cyst. Cause was probably congenital as patient never underwent any surgery or procedure in the past.

Discussion

Spinal arachnoid cysts are rare, so an algorithm to diagnose them solely on the basis of common presenting symptoms would be impractical. Most spinal arachnoid

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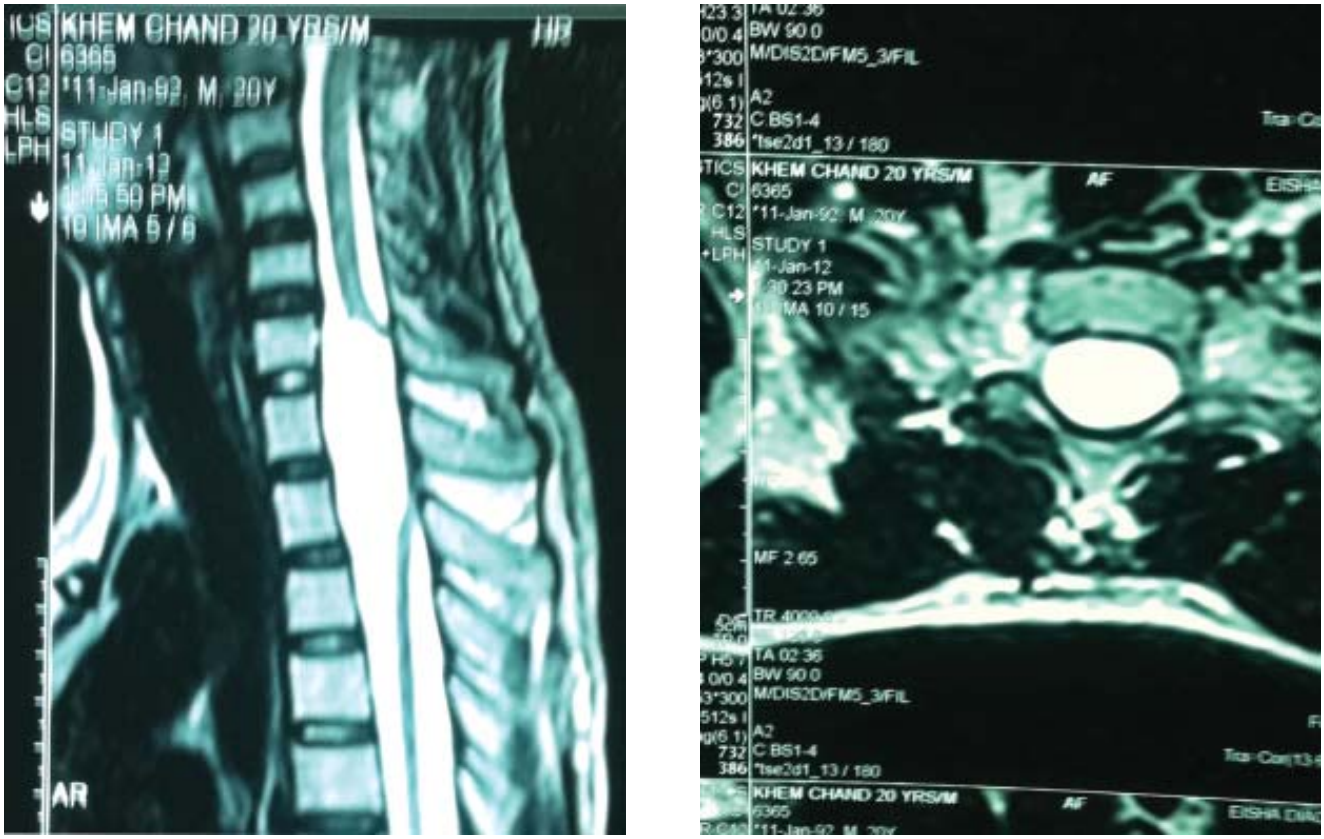

Fig. 1 - 2: *MRI showing arachnoid cyst in both longitudinal and transverse view of spine.*

cysts are asymptomatic and are discovered incidentally on magnetic resonance imaging (MRI) or myelography performed because of neck or back pain, myelopathy, or radiculopathy[8]. Whenever an arachnoid cyst is discovered, one must determine whether the cyst – or another problem – is actually causing the symptoms. If treatment is to succeed, the clinical presentation must correspond to the radiographic findings. Although most arachnoid cysts are found by MRI, it is inappropriate to initially order MRI to evaluate a cyst's common presenting symptoms (e.g., back pain, radiculopathy). Plain radiography should be done first. Although arachnoid cysts are composed of fluid and soft tissue, which are not easily detectable on plain films, subtle and indirect signs of a chronic, large cyst may be visible[5]. MRI is the next step if plain radiographs do not reveal bony abnormalities that could explain a patient's symptoms. MRI is the most sensitive and specific study for detecting a spinal arachnoid cyst[6,11] and for assessing the extent of the cyst wall. Intra venous gadolinium contrast can help distinguish between cystic tumours, synovial cysts, and arachnoid cysts. On T1- and T2-weighted images, the signal within a cyst has the same intensity as cerebrospinal fluid. Further studies help characterise the lesion.

Diffusion-weighted MRI can help differentiate an epidermoid cyst from an arachnoid cyst. It may also help differentiate a cyst from an abscess or tumour. Diffusion-weighted MRI can also help evaluate spinal cord atrophy and inflammatory changes[1,6,11]. Myelography or computed tomographic (CT) myelography were used to further characterise the form and structure of spinal arachnoid cysts discovered on MRI. CT myelography is also invaluable for imaging the spine of patients who have contraindications to MRI. For incidentally discovered spinal arachnoid cysts that cause no symptoms – i.e., most of them – surgery is not recommended. Yearly imaging should be done to detect any new abnormality and determine whether the cyst is truly benign. If symptoms arise, re-evaluation of the cyst with MRI should be immediately undertaken. For a patient with symptoms, treatment offers an excellent chance of neurologic recovery. Although aspiration may intuitively seem like the best initial approach to management, it only temporarily improves symptoms. However, percutaneous aspiration under fluoroscopic guidance may be appropriate for determining whether a cyst is causing a patient's symptoms and thereby predicting whether surgery can help. Surgery should

be undertaken only after careful consideration, as post-operative complications, though uncommon, may be very troublesome for both the patient and the surgeon. The standard treatment of an isolated spinal arachnoid cyst is complete surgical removal of the cyst[1]. Surgery typically results in excellent outcomes in terms of resolution of symptoms, and is effective across a large range of cyst sizes. Unfortunately, not all isolated spinal arachnoid cysts can be fully resected, owing to their location or to intra-operative findings such as extensive adhesion of a cyst to the spinal cord. In such cases, fenestration of the cyst wall, percutaneous drainage, or shunting the cyst into the peritoneal cavity may relieve symptoms[1-3,6].

Conclusion

Arachnoid cyst, though mostly rare and asymptomatic, must always be kept in mind during evaluation of paraparesis and back pain. If found and causing symptoms, early surgical removal of arachnoid cyst results in dramatic improvement.

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"A wise man will make more opportunities than he finds."

– FRANCIS BACON.

CASE REPORT

JIACM 2015; 16(1): 70-1

Headache as a presenting feature of Gullain Barré syndrome

SH Talib, Manjiri R Naik**, Rahul Sainani***, Nilrohit Paike*****

Abstract

Gullain Barré syndrome is an immune-mediated inflammatory disorder of the peripheral nervous system that produces rapidly progressive demyelination and axonal loss. Unexplained headache as a presenting symptom of GBS has been extremely rare in literature. However, only 2 cases in English language literature have been reported earlier by Kanel et al (2011). The patient, besides having headache, was noted to have isolated ptosis without ophthalmoplegia, and subsequently developed descending weakness. The ptosis as an initial occurrence without ophthalmoplegia in GBS is also extremely rare. We are presenting a case of Gullain Barré syndrome with such rare presentations of ptosis and headache as initial features of the disease.

Keywords: Headache, ptosis, Gullain Barré syndrome.

Case report

A 40-year-old woman with the medical history of type 2 diabetes mellitus controlled on oral hypoglycaemic agents presented with bilateral intractable temporo-occipital throbbing headache for the past 15 days. 8 days before admission to our hospital, she had neurologic and psychiatric consultations and was provided palliative therapy with analgesics and antipsychotics without any fruitful outcome. On presentation, she was alert and fully oriented and persistently complaining of severe headaches and generalised weakness. She had no vomiting, diplopia. General examination was unremarkable. Neurologic examination on presentation showed ptosis (right side) with global depressed deep reflexes except left ankle which was normal with preserved distal motor strength and 3/5 in proximal group. By day 3, patient again had neuropsychiatric problems in the form of anxiety, emotional disturbances, feelings of hopelessness, and depressive symptoms. She denied any bladder or any sensory abnormalties, or any apparent difficulty in breathing. However, her single breath count was 10 to 12 per min. Fundoscopy was normal. Lab findings of haemogram magnetic resonance imaging of brain along with magnetic resonance venography were normal. Cerebrospinal fluid examination showed albumino-cytologic dissociation. CSF protein: 115 mg%, sugar: 63 mg%, chloride normal, blood sugar at the time of lumbar puncture: 116 mg%. Microscopic examination revealed 3 to 4 lymphocytes per high power field. Nerve conduction studies revealed slow conduction, demyelination consistent with the diagnosis of polyneuropathy and axonopathy. She was provided with intravenous immunoglobulin in the dose of 400 mg/kg/day for 5 days. She showed improvement in her neuropsychiatric condition remarkably, and her headache disappeared altogether. However, her ptosis and limb weakness persisted, though improved. The patient was discharged on request in a stable condition after 10 days.

Discussion

GBS is an immune-mediated heterogeneous condition commonly characterised by combination of limb parasthaesias, generalised weakness and areflexia with motor, sensory, and autonomic dysfunction. The immuno-pathologic findings being endoneural inflammation in the spinal nerve roots, distal nerve root segments, or around nerve entrapment sites. The target antigens are perhaps common to axon, myelin sheath, or both. The psychiatric symptoms are not uncommon in persons with GBS which develop during early period of the disease[1]. Psychiatric symptoms include anxiety, depressive symptoms, reactive psychosis, hopelessness; and these features may occur independently or in combinations as a feature of subacute confusional state[2]. Our patient has had neuropsychiatric abnormalties in the form of anxiety, emotional disturbances, feelings of hopelessness, and depressive symptoms. The features were reviewed by a senior physician and through the staff and patient's family members. Our patient received tricyclic antidepressants and benzodiazepines and showed modest improvement with this therapy which was also combined with immunoglobulins. The observation suggests that a person with anxiety and affective lability in GBS may benefit from the judicious use of pharmacotherapy with TCAs and benzodiazepine combinations and immunoglobulins. Ocular muscle weakness may provide a challenge to distinguish Gullain

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Barré syndrome from myasthenia gravis. Ptosis as an initial presentation of Gullain Barré syndrome without ophthalmoplegia has been extremely rare[3]. Kanhel (2011)[4] reported 2 cases in a week who presented in the emergency department for unexplained headaches. The lumbar puncture revealed the unexpected findings of albumino-cytological dissociation and further investigations in the case led to the diagnosis of GBS variant. Headache as a presenting symptom of GBS has been extremely unusual as aptly noted in the world literature[4,5]. The present case under discussion had only headache as the presenting symptom of GBS. Inflammed cranial nerves, spinal roots, peripheral nerves may cause aching and throbbing pains. Any patient with acute unexplained headache and areflexia with or without ptosis, a possibility of GBS needs to be considered as a major differential diagnosis.

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"I say unto you, joy and sorrow are inseparable.
Together they come, and when one sits alone with you at your board,
remember that the other is asleep upon your bed."

– KAHLIL GIBRAN.

CASE REPORT

JIACM 2015; 16(1): 72-4

Primary extra-nodal non-Hodgkin's lymphoma of the orbit

*Gouranga Santra**

Abstract

Primary lymphoma arising from the orbit is a rare presentation. Primary orbital lymphoma is commonly a B-cell type of non-Hodgkin's lymphoma (NHL). Among the B-cell NHL arising from ocular adnexa, mucosa associated lymphoid tissue (MALT) lymphoma is the commonest, followed by follicular lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma. Commonest site of origin of orbital NHL is superior orbit behind the orbital septum.

A 30-year-old young male presented with orbital swelling and proptosis. CT scan revealed a soft tissue mass arising from temporal aspect of left orbit, attached to the orbital walls, without any bony destruction. Biopsy confirmed it to be a case of primary NHL of diffuse large B-cell type.

Keywords: Primary lymphoma, orbit, diffuse large B-cell lymphoma.

Introduction

Primary lymphoma arising from orbit is a rare presentation. It is commonly of B-cell type. Among the B-cell non-Hodgkin's lymphoma (NHL) arising from ocular adnexa, mucosa associated lymphoid tissue (MALT) lymphoma is the commonest histologic variant, followed by follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma[1]. We report a rare case of primary orbital lymphoma of diffuse large B-cell type presented with left orbital swelling, proptosis, and visual loss.

Case report

A 30-year-old male presented with painless left orbital swelling of one-and-a-half years duration. The swelling first appeared in temporal aspect of left orbit with a size approximately 2.5 x 2.5 cm. It gradually enlarged in size. Patient gave no history of fever, night sweats, weight loss, past or contact history of tuberculosis, or any unprotected sexual exposure. He did not give any history of shortness of breath, pruritus, abdominal, chest or bone pain. Prior history of exposure to radiation was absent. At the time of examination, the patient had mild pallor. The swelling was 7.0 x 5.0 cm, spherical, involving mainly the lower and outer aspect of the left eye, and extended to involve the cheek (Fig.1). It was firm in consistency throughout, nontender, attached to superficial skin and underlying structures without any discharging sinus or overlying ulcer. Superficial temperature was not raised, no thrill or pulsation was noted, and no bruit was found. Systemic examination did not reveal any lymphadenopathy, hepatosplenomegaly, mediastinal dullness or features of

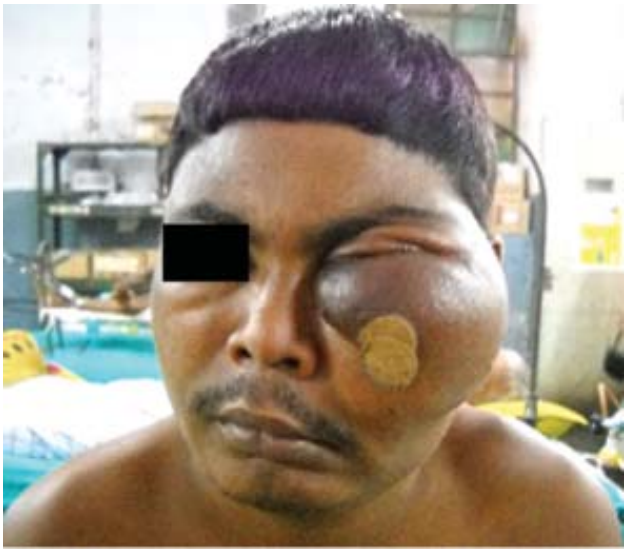

***Fig. 1:** Orbital swelling involving the left eye extending to maxillary region.*

superior vena caval obstruction. Visual acuity could not be tested in left eye due to inability to open it. Right eye showed no abnormality. There was no involvement of any cranial nerves. Peripheral blood smear showed no abnormal cells. Haemoglobin was 9.8 g/dl, serum LDH was 677 U/l. Other routine laboratory tests like sugar, urea, creatinine, liver function test, uric acid, calcium, chest X-ray, echocardiography, and upper gastrointestinal endoscopy were normal. HIV serology was nonreactive. CT scan of skull with contrast revealed a homogeneous soft-tissue mass arising from the temporal aspect of left orbit, attached to the orbital walls, without any bony destruction (Fig. 2 and 3). X-ray skull revealed no lytic lesion (Fig. 4). Fine needle aspiration cytology (FNAC) from the lesion revealed high cellularity with immature large

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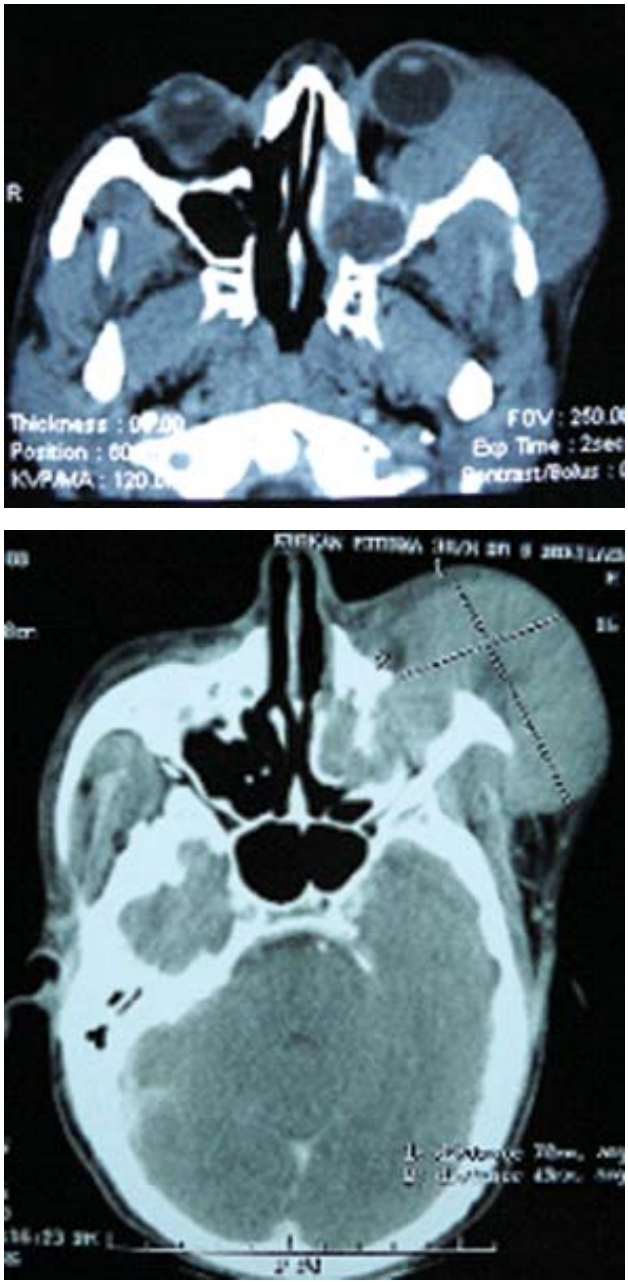

Fig. 2 and 3: *Contrast-enhanced CT scan of orbit showing a soft-tissue mass (7 cm x 4.9 cm) involving the left orbit.*

lymphoid cells with few mature lymphocytes in the background suggestive of diffuse large cell NHL. Later, incision biopsy and histological examination showed heterogeneous neoplastic cells with predominantly large cells with moderately abundant pale or basophilic cytoplasm, large round-ovoid nuclei, prominent nuclear membrane with margination of vesicular chromatin, and multiple prominent basophilic nucleoli, consistent with intermediate grade diffuse large B-cell variant of NHL. Immunohistochemistry showed positive result with CD19, CD20, and CD22. Tumour was BCL-6 positive but MUM-1 negative. CT scan of abdomen, pelvis and thorax showed no enlarged lymph nodes or organomegaly. Bone marrow trephine biopsy revealed no marrow involvement. Serum protein electrophoresis and serum β2 microglobulin were within normal limits. The patient was categorised under NHL stage IE. He was treated with combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen; and responded favourably with regression of the swelling.

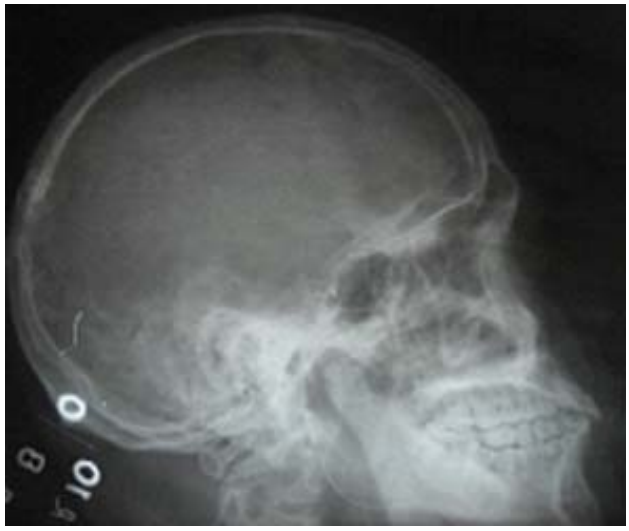

Fig. 4: *X-ray skull right lateral view showing no bone destruction.*

Discussion

A primary lymphoma arising from the orbit is a rare presentation. Onset of primary orbital NHL is mainly in the sixth or seventh decade with a slight female preponderance. However, in Indian studies, male preponderance was mentioned[2]. It may occur as a secondary manifestation of systemic lymphoma or may arise discretely. Orbital swelling and proptosis are the two commonest presenting features but often it may present as a salmon-patch like protrusion in the conjunctiva. Among the histologic variants, B-cell type is commonest. In one case series from north-east India, the commonest histologic variant was found to be B-cell type (89%) of NHL followed by T-cell (5%) and lymphoepitheloid (5%) variant[3]. Among the B-cell NHL arising from ocular adnexa, MALT lymphoma is the commonest histologic variant, followed by follicular lymphoma, DLBCL, mantle cell lymphoma[1]. The commonest site of origin of orbital NHL is the superior orbit behind the orbital septum[4]. In 30 to 40% cases, it arises from the lacrimal gland causing substantial degree of proptosis[4]. In our case, lacrimal gland was not involved. It may also arise from eyelids, conjunctiva, or orbital musculature. DLBCL may be

associated with large destructive masses involving adjacent structures such as paranasal sinuses[1]. Our patient had no bony destruction.

Primary orbital NHL shows favourable prognosis if diagnosed early. Total or subtotal surgical excision followed by radiotherapy and/or chemotherapy showed better outcome[5]. Primary orbital NHL particularly MALT lymphoma without systemic involvement shows a better response to radiation than other extranodal NHL. Major side-effect of radiotherapy is cataract that develops 3 - 8 years after radiation. Primary treatment modality of diffuse large B-cell NHL is combination chemotherapy. Radiation – though often applied – has an unclear role. Rituximab with CHOP regimen has shown better outcome in the elderly.

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CASE REPORT

JIACM 2015; 16(1): 75-9

Kartagener's syndrome – A case report with review of literature

Ishrat Hussain Dar, Showkat Hussain Dar*, Samia Rashid***

Abstract

Lower respiratory tract infections are common in our society. Recurrent lower respiratory tract infections demand a thorough investigative workup as the cause may range from general impairment of the immune system to abnormalities of the mucous or the cilia. Reported here is a childless young married female with recurrent lower respiratory tract infections from childhood who after examination was found to have dextrocardia. Detailed evaluation revealed situs inversus, chronic sinusitis, and bronchiectasis which favoured a diagnosis of Kartagener's syndrome. Kartagener's syndrome is an inherited disorder transmitted in an autosomal recessive manner with variable penetrance. Though there is no specific treatment for this condition, a failure to recognise it leads to an unnecessary burden on the patient as well as the hospital by way of frequent, repeated admissions and investigations leading to complications by way of inappropriate treatment.

Key words: Kartagener syndrome, dextrocardia, situs inversus, bronchiectasis, sinusitis, sterility, autosomal recessive.

Introduction

Kartagener's syndrome is an autosomal recessive inherited disorder characterised by a triad of situs inversus, sinusitis, and bronchiectasis. Males and females are affected equally. The complete syndrome has high familial evidence appearing only in one generation and multiple siblings may have various combinations of its components which do not appear in their children. These features and the high incidence of consanguinity among the apparently normal parents of affected children support the contention that genetic abnormality is carried as an autosomal recessive gene. This disorder affects the activity of proteins important to the movement of cilia especially in the respiratory tract and the spermatozoa leading to defective clearance of mucus and resulting in recurrent respiratory tract infections occasionally progressing to lung abscesses, anosmia, and sterility. It has been suggested that Kartagener's syndrome be listed as a subset of a broader category of diseases called as the immotile cilia syndrome.

Case report

A 28-year-old married female reported to the out-patient department of our hospital with complaints of recurrent lower respiratory tract infection in the form of productive cough, occasional streaky haemoptysis, breathlessness on exertion, headache, and fever. Though the symptoms were mostly intermittent and used to subside with a course of antibiotics which she would by and large procure from the local pharmacy but had never undergone a full, proper and thorough evaluation to look into the cause of her disease until she landed in our teaching hospital with a progressive sustained increase in the above symptoms. Fever was mostly moderate to high grade, intermittent, and occasionally continous, sometimes associated with chills and rigors. Cough was productive, sputum being variable in colour ranging from mucoid to frankly purulent at times with an average production of more than 200 ml/day that would worsen during the cold season. Breathlessness, by and large, always accompanied the cough but of late had worsened so much so as to cause the patient to experience it even at rest, prompting her to go for a thorough investigation. Headache was usually nocturnal, global in distribution, more on lying down and with some relief towards the mid-day. On examination, the patient was tall, of average build, poorly nourished and paler than normal. Streaks of grey hair with some areas of sparse hair were present. Small bilateral cervical lymph nodes measuring about 1 x 1 cm, firm in consistency, without inflammation of the overlying skin or fixity to the underlying structures, were found. Clubbing of the fingers was present with a positive Schamroth's sign bilaterally. Cyanosis of the tongue was noted. No flap was elicited. Mild pedal oedema was noted on both the shins. Vital signs revealed a pulse of 84/mt regular, BP of 110/76 mmHg and a respiratory rate of 20/min. Examination of the chest revealed bilateral coarse crepitations at the bases. Apex was noted on the right side in the 5th intercostal space in the mid-clavicular line. Heart sounds were heard on the right side without any thrill or murmur. The upper border of the liver was noted in the left 6th intercostal space and tympanitic note of the fundal gas was encountered in the right 7th intercostal space. ENT examination revealed evidence of rhinosinusitis with bilateral hypertrophied (middle) engorged bluish

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turbinates with pale mucosa of the nasal cavity. Nasal patency on the right side was reduced. The rest of the clinical examination was normal. A tentative diagnosis of dextrocardia, situs inversus, and bronchiectasis was made and a possibility of Kartagener's syndrome was kept in mind. Investigation revealed a Hb of 11 gm%, TLC of 16,000/cmm with a DLC of 88% polymorphs, 10% lymphocytes, platelets 1.34 lacs/cmm, and ESR of 58 mm/1st hr. Blood sugar, kidney function tests, liver function tests, electrolytes, and urine examination were normal. Sputum for AFB (3 samples) and Gram's stain were negative for organisms; and sputum for culture failed to grow any organisms, possibly because of antibiotic use. Mantoux test was negative. X-ray chest showed dextrocardia with bilateral lower zone bronchiectasis (Fig. 1). Anti-nuclear antibody (ANA) and anti-double stranded DNA (anti-ds DNA) were negative. HRCT chest showed a right-sided aortic arch with dextrocardia with situs inversus and a left lower lobe resolving consolidation and bilateral bronchiectasis (Fig. 2a and 2b). Spirometry revealed an obstructive pattern. ECG showed qS pattern and T wave inversion in lead I, p wave inversion in I and avL with other features of dextrocardia like a progressive decrease in R wave from V1 to V6 in the left-sided chest leads and increase in R amplitude from V1 to V6 in right-sided chest leads (Fig. 4). Echocardiography showed structurally normal heart with situs inversus, dextrocardia with base to apex – right, intact septae without PDA, COA and no gradient in the RVOT or LVOT. A CT scan of the

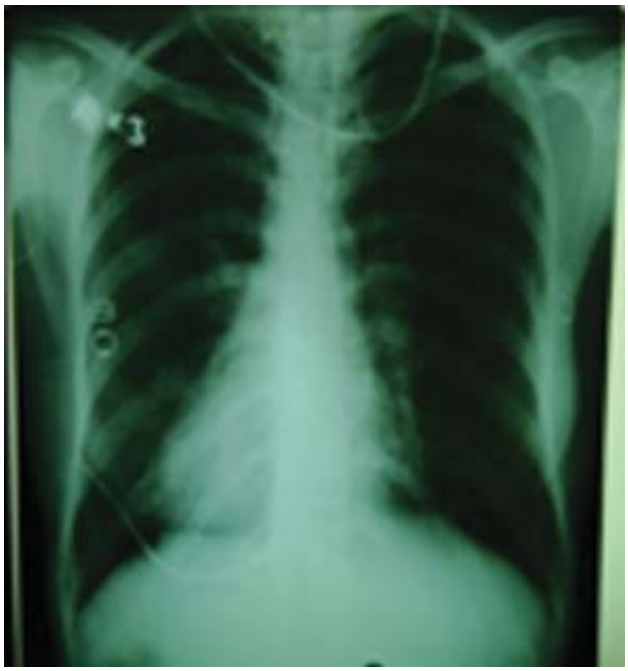

Fig. 1: *X-ray chest of the patient depicting dextrocardia with bilateral lower zone bronchiectasis.*

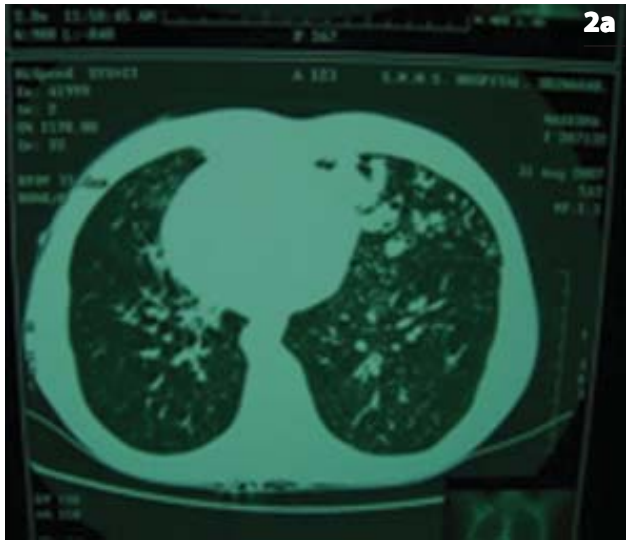

Fig. 2a and 2b: *HRCT chest showing a right-sided aortic arch with dextrocardia with situs inversus and a left lower lobe resolving consolidation and bilateral bronchiectasis.*

paranasal sinuses revealed pansinusitis and hypertrophied right inferior turbinate (Fig. 3a and 3b). Ultrasonography of the abdomen revealed situs inversus with liver on the left side and spleen on the right with structurally normal organs except a small 5 mm calculus in the middle cortex of the left kidney. With this history and clinical examination supplemented by investigations a diagnosis of Kartagener's syndrome was made and the patient was started on broad spectrum antibiotics, bronchodilators, mucolytics, and aerosol nebulisation thrapy with progress in the resolution of symptoms. On regular follow-up, the patient has since been doing well with an improved sense of well-being subjectively and

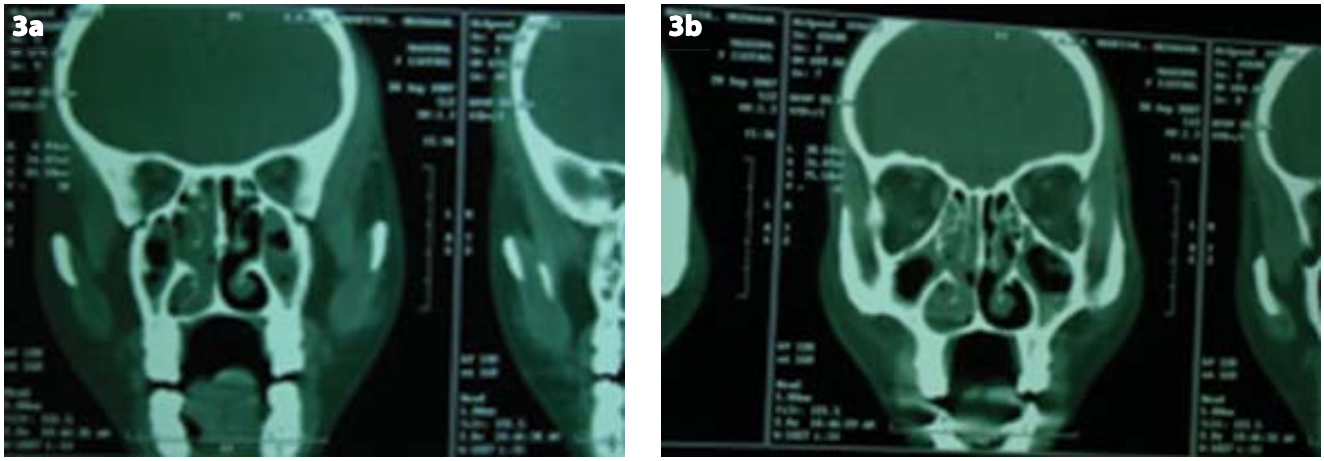

Fig. 3a and 3b: *CT scan of the paranasal sinuses revealing pansinusitis and hypertrophied right inferior turbinate.*

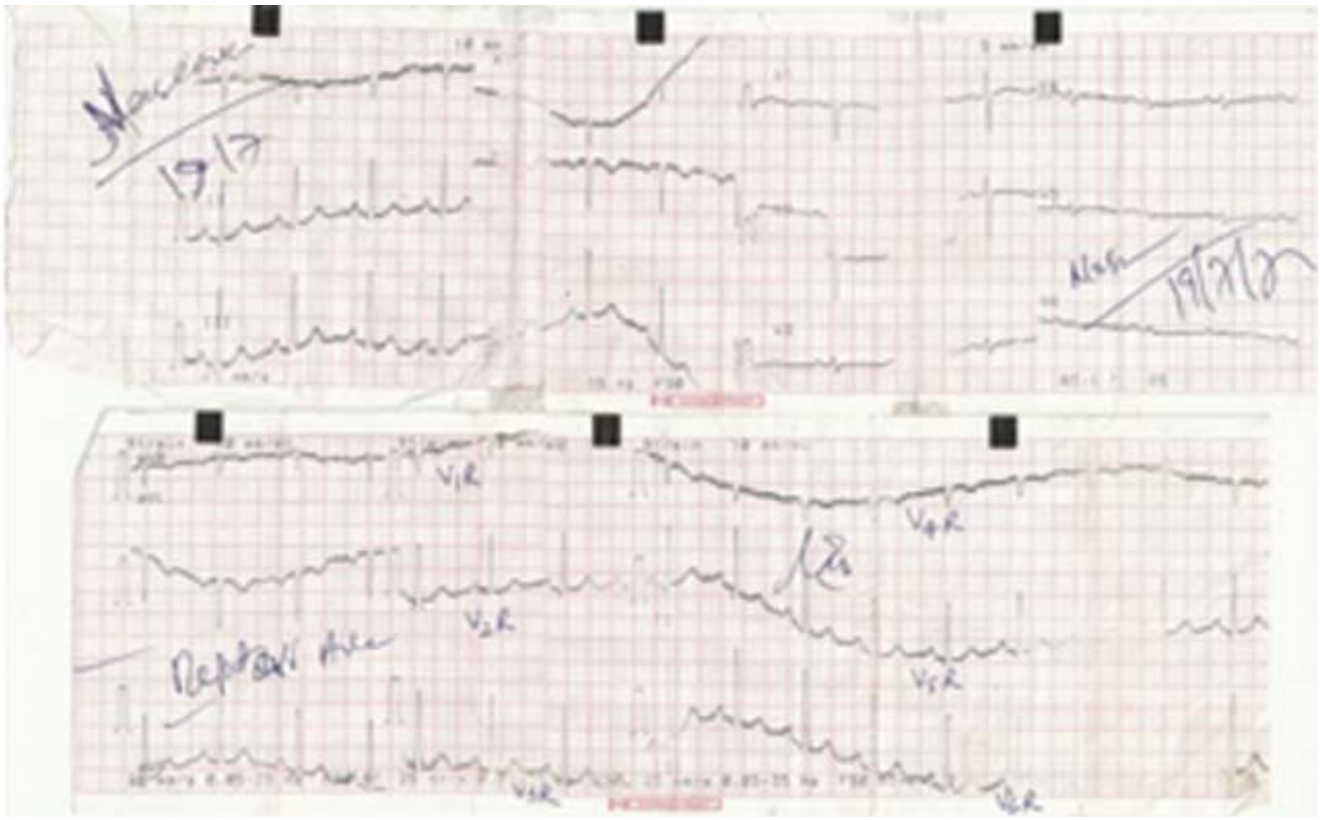

Fig. 4: *ECG showing qS pattern and T wave inversion in lead I, p wave inversion in I and avL with other features of dextrocardia like a progressive decrease in R wave from V1 to V6 in left-sided chest leads and increase in R amplitude from V1 to V6 in right-sided chest leads.*

objectively.

Discussion

Kartagener's syndrome is an autosomal recessive disorder characterised by dextrocardia, situs inversus, bronchiectasis, and sinusitis first described by Siewert in 1903[1] and therefore some people call it Siewert syndrome as well. This was followed by another report by Oeri in 1909[2]. Kartagener reported four cases in 1933[3], and seven more in 1935[4]. He was the first to point out that the occurrence of the triad was more than coincidental and that the incidence of bronchiectasis and sinusitis was proportionately more frequent in persons with situs

inversus than in other persons suggesting a congenital aetiology. Kartagener's syndrome is a rare disorder with an incidence of 1 in 15,000 to 1 in 30,000 people[5]. Sinusitis, bronchiectasis, situs inversus and male/female infertility occurring in this condition are attributed to abnormal ciliary motility. Cilia may be immotile or may show uncoordinated and inefficient movement patterns. The immotility is due to a variety of ultrastructural defects in the respiratory cilia and the sperm tail. Though concordance between abnormalities of the cilia and sperm tails is the rule, yet some occasional discordance is noted because of variable phenotypic presentations. Ciliary movement disorders may be congenital or acquired. Congenital ciliary disorders are labeled as primary ciliary dyskinesias (PCD)[6]. Approximately one half of the patients with PCD have situs inversus. Patients with PCD and situs inversus are referred to as having the Kartagener's syndrome. Afzelius[7] was the first to recognise the relationship between Kartagener's syndrome and male infertility when he observed lack of dyenin arms in the sperms and cilia of four subjects and the identification of these abnormalities led to the more descriptive "term immotile cilia syndrome" in place of Kartagener syndrome. Abnormalities of radial spokes and microtubules can also found in the cilia. In rare cases no structural ciliary abnormality is detectable even though the ciliary function is abnormal and the clinical syndrome is typical. Other synonyms for this disorder are primary ciliary dyskinesia and the dyskinetic cilia syndrome. The ciliary abnormalities prevent normal transport of mucus from the bronchial tree to the mouth resulting in serious impairment of the lung's defense mechanism and causing repeated sinopulmonary infections[8,9]. Males are generally infertile because of the immobile sperms; however, some males have completely normal spermatozoa, and reports of fertility have also been seen in literature[10]. Presence of rhinitis, chronic otitis, nasal polyposis, and opacified sinus cavities with pansinusitis in the form of involvement of maxillary, frontal, and ethmoid sinuses is a cardinal feature of this syndrome which later on leads to parosmia and anosmia as well[11]. Situs inversus – a condition in which the internal organs are located on the opposite side of the body away from their normal position – is the most striking and earliest feature of Kartagener's syndrome. When the inversion involves all the thoraco-abdominal viscera, it is called as situs inversus totalis. Situs inversus can be classified as situs inversus with dextrocardia or situs inversus with levocardia depending upon the direction in which the cardiac apex points at birth. In levocardia the base to apex axis points to the left and in dextrocardia the base to apex axis points to the right as was seen in this case as well. Afzelius[7] correlated situs inversus and cilia immotility explaining that the defects in embryonal cell motility could be responsible for non rotation of some abdominal viscera and that normal ciliary beating is necessary for visceral rotation during embryonal development. In patients with PCD, half of the patients will have situs inversus (will be cases of KS) and the other half normal situs because of random rotation[12,13]. Bronchiectasis – another component of the syndrome – develops after birth with irreversible, localised dilatation of the bronchial tree which is inflamed and easily collapsible resulting in airflow obstruction and impaired clearance of secretions. This results in colonisation and infection with pathogenic organisms contributing to the purulent expectoration observed in patients with KS. As a result of bronchial injury a vicious cycle of bronchial damage, dilatation, impaired clearance of secretions, recurrent infection and more bronchial damage is seen. The classic triad of chronic cough, excess purulent sputum production and repeated infections are seen in severely affected patients. Haemoptysis is common and affects 50% of the patients. Bleeding originates in the dilated bronchial arteries and less common symptoms include dyspnoea, pleuritic chest pain, wheezing, fever, and weight loss. Significant airway obstruction may occur as a result of bronchitis, bronchiolitis, or emphysema that accompanies bronchiectasis. Recurrent pneumonias are common and X-ray as well as the CT scan of the chest are helpful. X-ray chest demonstrates normal or a thickening of the bronchial wall but a HRCT chest may show bronchiectasis and an internal bronchial diameter larger than the diameter of the accompanying pulmonary artery, a lack of tapering of the bronchi, and the presence of bronchi in the outer third of the lung parenchyma[14,15]. Bronchiectasis is more prevalent in people with situs inversus and reported as between 12 - 25% in patients with situs inversus[16]. At least 90% patients present before the age of 14 years. From early childhood the symptoms are frequent colds, increased nasal secretion, respiratory allergies, headache, fever, and recurrent pneumonic infections. The common organisms implicated in causing most of the infections in KS have been found to be *Stretococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Pseudomonas aeruginosa*[17,20]. The diagnostic criteria recommended for this syndrome are a history of chronic bronchial infection and rhinitis from early childhood combined with one more of the following features: (a) situs inversus or dextrocardia in a patient or a sibling, (b) living but immobile spermatozoa, (c) tracheobronchial clearance which is absent or nearly so, (d) cilia with ultrastructural defects characteristic of this syndrome. Our case had all features except immotile sperms as she was a female. Demonstration of abnormal ciliary movement needs electron microscopic studies of biopsies obtained from the nasal mucosa or the trachea

making this procedure invasive. Since the diagnosis is by and large clinical and supported by non invasive investigations like CT/echo/USG/ECG/X-ray, the nasal biopsy is hardly required except in experimental specialised centres. Some unusual associations of KS have been reported in literature as KS with allergic bronchopulmonary aspergillosis[18], KS with infundibular pulmonic stenosis, chronic renal failure and azoospermia[19], KS with multiple lung abscesses[20] and KS as an unusual cause of respiratory distress in the new-born[21]. Treatment of this rare congenital disorder includes antibiotics (intravenous or oral), intermittent or continous used to treat upper and lower airway infections. Inhaled bronchodilators, mucolytics, and chest physiotherapy are used to treat bronchiectasis/lower respiratory tract infections. A role for inhaled or oral corticosteroids and recombinant DNA is anecdotal. Pneumococcal and H influenza vaccination is preffered and advised to decrease both the severity and frequency of infections. Surgical care includes tympanostomy tubes to reduce recurrent infections/conductive hearing loss. Endoscopic sinus surgery with a nasal antral window underneath the inferior turbinate may improve upper and lower respiratory tract symptoms[22]. Pulmonary surgery in form of lobectomy, lingulectomy and or segmentectomy have been tried with some success in selected cases[23]. Lung transplantation and heart-lung transplantation may provide hope of prolonging life in severe cases[24,25].

Conclusion

To conclude, it is important to consider the diagnosis of Kartagener syndrome in a child or young adult who presents with a history of recurrent respiratory tract infections coupled with chronic sinusitis and febrile illness associated with impaired mucociliary clearance and sterility or impaired fertility.

Conflict of interest statement

The authors have no conflict of interest – whether financial or otherwise – in the preparation of this manuscript for publication.

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CASE REPORT

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Non-small cell lung carcinoma in a young adult manifested by non-retractile vomiting

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Abstract

Lung adenocarcinomas in the young population below age of 30 years are extremely rare; only individual cases have been reported previously. We report a 25-year-old Indian male with non-small cell lung carcinoma (NSCLC) stage IV, T4N2M1. He presented with non-retractile vomiting secondary to non-communicating hydrocephalus. Treatment following corticosteroid therapy was started to relieve the raised ICT and a positive response was seen. After symptomatic relief patient was shifted to the oncology unit. The current case report reinforces that similar situations are bound to arise again in the future with changing trend and the trend of increasing rate of NSCLC in younger patients.

Key words: Non-small cell lung carcinoma, pulmonary adenocarcinoma, brain metastasis, young adult.

Introduction

Recurrent projectile vomiting suggests diverse aetiologies involving central nervous system (CNS) infections. They may range from infectious, genetic to organic aetiology. The peak age for NSCLC is 50 years to 60 years[1]. Lung carcinomas in patients around 25 years of age are extremely rare. Here, we report the case of a 25-year-old boy with asymptomatic pulmonary adenocarcinoma with brain metastases T4N2M1 initially presenting as sudden non-retractile vomiting.

Case presentation

Our patient was 25-year-old married male, the first child of non-consanguineous healthy parents, both Indian; his other two siblings were healthy. No case of carcinoma had been observed in the grandparents. He was born after an uneventful pregnancy and showed normal development. He never smoked nor abused other substances, nor was he exposed to tobacco smoke, chemicals, or irradiating toxins.

He presented with a one-and-a-half months history of non-retractile vomiting, 4 - 5 episodes a day, projectile, consisting of food materials, not associated with nausea or abdominal discomfort, not blood stained, no history of recent diarrhoeal illness and fever. For this he consulted two physicians prior to visiting our centre, but did not get any relief. Clinical examination was done and tandem walking was positive, finger-nose test was positive on left side, dysdiadochokinesia was positive on left side suggestive of cerebellar involvement with single left side inguinal lymphadenopathy of superficial group, size 1 cm, firm, rubbery with hyperpigmented macules all over the upper back. Otherwise, the patient was in a stable condition with a normal examination status.

He presented with a chest X-ray PA view, done 10 days prior to visiting us. Chest X-ray showed a lobulated soft tissue mass in the right mid lung field and bilateral pulmonary nodules with bilateral multiple small nodules in both lung fields (Fig. 1). Radiologically, these lesions were interpreted as malignancy with lung-to-lung metastasis. Suspicion of central nervous system involvement (CNS) led to magnetic resonance imaging (MRI) of his brain followed by contrast-enhanced computed tomography (CECT) of his chest (Fig. 2, 3 and 4).

MRI brain showed multiple, intra-axial, soft-tissue signal intensity lesions of variable sizes. Variable adjacent vasogenic oedema was noted in bilateral cerebral and cerebellar hemispheres; larger right cerebellar lesion and left periventricular lesions had subacute blood products within and measured 36 × 35 × 35 mm and 30 × 25 × 25 mm respectively. Infra-tentorial lesions had significant mass effect over the aqueduct and fourth ventricle leading to dilataion of the third and lateral ventricles with periventricular white matter CSF ooze. MRI imaging was suggestive of multiple supra- and infra-tentorial, intra-axial space occupying lesions causing non-communicating hydrocephalous with possibilities of fungal granuloma, tuberculoma, and neoplastic secondaries.

CECT chest showed heterogeneously enhancing soft-tissue density with irregular margin of size 38 × 29 × 28 mm in the anterior mid-lung filed. Multiple small subcentimeter size nodular opacities were distributed in almost all segments of both lungs. Multiple enlarged lymphnodes of 10 × 20 mm size were noted in pre- and paratracheal, carinal, subcarinal and right infrahilar regions suggestive of primary lung carcinoma with bilateral lung metastases. Histological analysis showed a non-small cell adenocarcinoma lung (NSCLC), stage IV, T4N2M1 (Table I). Complete laboratory and clinical work-up showed no infections, immunodeficiency, or drug addiction. The

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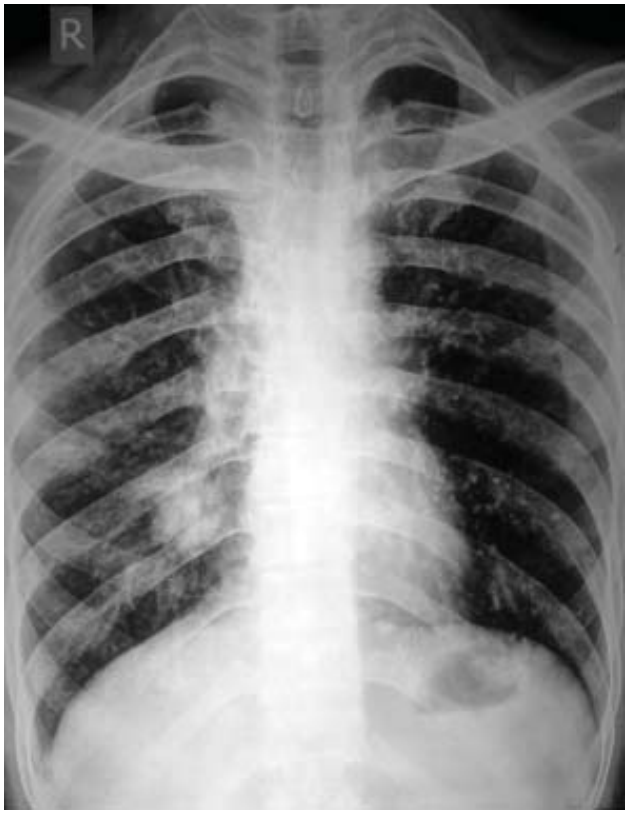

Fig. 1: *Chest X-ray showed homogeneous opacity in the right lower lung zone with multiple nodular opacities in bilateral lower lung zones.*

patient responded to corticosteroids and his symptoms of vomiting were relieved. Thereafter, the patient was transferred to the oncology cell for further management after counselling regarding his disease.

Table I: Primary tumour.

T4	With separate tumour nodules in a different ipsilateral lobe.	
Regional lymph node involvement		
N2	Ipsilateral or subcarinal mediastinal nodes Ipsilateral supraclavicular nodes.	
Metastatic involvement		
M1	Metastases present.	
Stage	*TNM*	5-year survival rate (%)
IV	T4 N2 M1	< 5

Discussion

Lung cancer is the commonest lethal malignant disease worldwide, accounting for 28% of all cancer deaths, mostly occurring after the fifth decade of life[2,3,4]. Non-small cell lung cancer (NSCLC) represents 80% of all lung cancers with occurrence age group of 50 - 80 years[5]. Only 0.1 - 0.4% of all lung cancer cases occur at age below 30 years as reported by previous studies[6]. Previous studies show only 2 published clinical series on lung cancer patients younger than 30 years[7]. Of those patients in whom NSCLC is destined to develop, only 3% will present before the age of 45 years, and 9% before the age of 50 years[8]. One of the studies depicts 0.8% of patients under 30 years age group[9]. These findings suggest that lung cancer – adenocarcinoma of lung – rarely occurs in population below 30 years of age group[10,11,12].

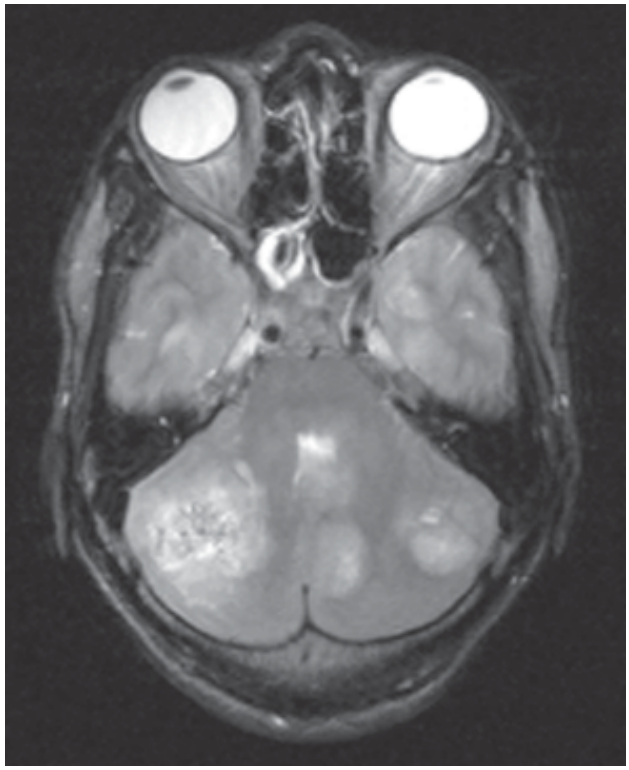

Fig. 2: *T2 weighted images showing multiple heterogeneously hyperintense lesions in the cerebellum, probable metastases.*

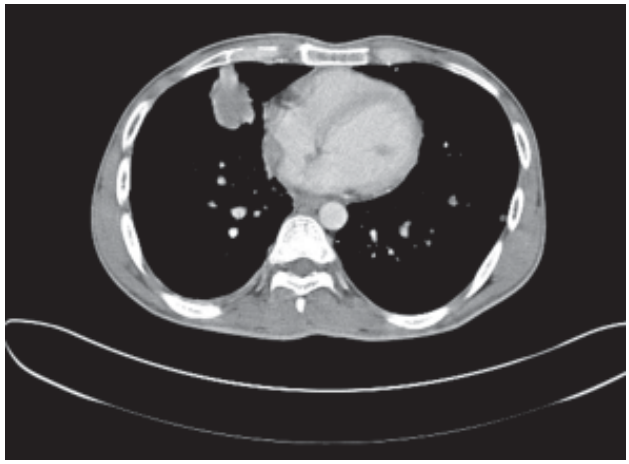

Fig. 3: *Homogeneously enhancing lesion seen in the medial segment of right middle lobe. The lesion turned out to be an adenocarcinoma on FNAC.*

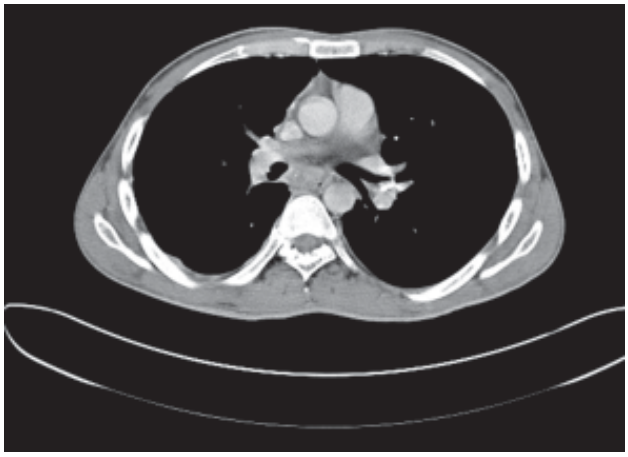

Fig. 4: *Multiple enhancing lymph nodes are seen in sub-carinal and bilateral hilar regions.*

Noted in never-smokers, adenocarcinoma has always been the predominant histological type[13]. There is a changing trend of higher incidence of adenocarcinoma in young patients[14]. Studies suggest that young patients are very likely to present with advanced disease[8,12]. Bilateral brain metastases occurs mostly in 30 - 50% of patients with (NSCLC) and confers upon the patient a worse prognosis and quality of life[15,16]. Despite bilateral multiple brain metastases leading to cerebellar dysfunction due to the gradually expanding tumour and associated oedema, the routine activity of our patient was not hampered as he was asymptomatic and thus leading to a late presentation in our clinic.

Presence of certain signs and symptoms in our case designate a distinct difference in the pathology and behaviour of lung tumours that occur in the young[3]. These were clubbing of nails in the patient, commonly found in smokers, despite of any history of smoking[17]. During brain metastases, neurological symptoms mostly occured due to the expanding mass, but rarely due to obstructive hydrocephalus as was found in the present situation. Absence of any pulmonary symptoms despite bilateral miliary metastases from lung to lung and presence of papilloedema, occurring in less than 10 per cent of patients at time of presentation, without any visual complaints.

To the best of our knowledge, the presence of NSCLC in an asymptomatic 25-year-old non-smoker male, with no family history of cancer, no past medical history, and no environmental or occupational risk factors associated with lung cancer, has not been previously reported.

Conclusion

Our case suggests that the changing trend of the disease may lead to deviation from the predefined pathway of presentation of the disease. This disease may present as a silent killer – as a wolf in sheep's clothing – for a long time without showing any presentation of the involvement of the system of origin and presenting as non-specific symptoms even in the advanced stage after brain metastases. Therefore, when an asymptomatic young patient presents with abnormal findings on X-ray chest, lung cancer should be considered in the differential diagnosis. The current case report reinforces that similar situations are bound to arise again in the future with changing trend and the trend of increasing rate of NSCLC in younger patients[7,10,11,14].

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CASE REPORT

JIACM 2015; 16(1): 83-4

A rare case of excessive watering from the left eye while eating

*AK Gupta**

Abstract

Different types of nerve injuries are described in the literature, like neuropraxia (physiological paralysis of conduction), axonotmesis (intra-thecal rupture of nerve fibres with intact sheath) and neurometosis (partial or complete division of nerve fibres and sheaths). In neuromatosis the regeneration is slow and varies depending upon the extent of injury; and during recovery, mal-distribution of fibres is well known – specially in case of mixed nerves.

A patient may present with multidimensional symptoms, but sometimes it may not be possible for the treating physician to diagnosis and treat. This case having been worked-up, the patient was explained the most possible cause of his problem on the basis of anatomical and physiological changes, which might have taken place after an accidental head injury, so that he could prepare himself to adopt this change in his lifestyle throughout his life.

Introduction

Tears are hypertonic fluid, secreted by lachrymal glands. Lachrymal glands are situated in the upper and outer quadrant of the orbit under the zygomatic process of the frontal bone. Under normal circumstances, secretion suffices for lubrication and cleaning of cornea and conjunctiva. In addition to this, the main gland plays a special role only upon special circumstances, e.g., irritation of conjunctiva; as a result of fear; certain emotional states, such as grief, disappointment and anger, etc. Normally lacrimation is induced by reflex action[1].

Salivary glands are mainly three: parotid, submandibular and sublingual. Parotid gland is located at the side of face, below and in front of ear. Submandibular gland in below and medial to the mandible, and sublingual is below the tongue in the floor of mouth. Salivation generally is in response to food in the mouth and it is found that the parotid gland contributes about 25%, submandibular about 70%, and only 5% sublingual. Normally, it is a reflex action in response to food[1].

The facial nerve is attached to the brain stem by 2 roots, motor and sensory. The sensory root is also called nervus intermedius of Wrisberg. Secretomotor parasympathetic fibres for lacrimal and salivary gland accompany nervous intermedius. Both the components along with other structures (8th cranial nerve and blood vessels) enter into internal acoustic meatus in the petrous part of temporal bone. The first part of the facial nerve moves lateral, secretomotor fibres to lachrymal gland forms a superficial petrosal nerve which enters in the pterygoid canal to sphenopalatine ganglion. The second part runs backward where its motor component gives a branch to stapedius muscle. The third part runs downward in the facial canal, 6 mm above stylomastoid foramen. It gives chorda tympani secretomotor fibres for salivary glands through submandibular ganglion[2,3].

Case report

A 26-years-old unmarried male presented with the h/o excessive watering (tears) from left eye while eating since the last 4 years. These tears used to start as he put food into his mouth and started chewing. Sometimes it became very difficult for him to eat the food. In 2008 (at the age of 21 years) he met with a road side accident and had sustained a fracture at base of skull with bleeding from left ear. For this he took treatment from PGIMER, Chandigarh, and fully recovered. Four to six months later he developed these symptoms, and for these he visited 7 - 8 health institutions, but had no improvement. He is non-diabetic and non-hypertensive.

On examination: pulse was 80 per minute; BP was 128/70 mm of Hg. His higher mental functions, speech, B/L cranial nerves, taste sensation over the anterior 2/3 and posterior 2/3 of tongue (on both sides), motor and sensory systems were normal. There was no neurological deficit. B/L eye examination was normal, regurgitation test was negative. From other systemic examination, nothing was contributory. Investigations: urinanalysis, haemogram, blood chemistry, CT scan, head and MRI brain was normal.

Discussion

Lachrymal reflex

Stimulus from cornea and conjunctiva → lacrimal branch of ophthalmic division (somatic sensory) to Pons →

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stimulus processed in lacrimal nucleus (near to superior salivary nucleus) → Pre-ganglionic parasympathetic fibres passes along nervus intermedius → in the auditory canal along with facial and vestibular nerve. Fibres pass by the side of the geniculate ganglion → greater superficial petrosal nerve → nerve of pterygoid canal → sphenopalatine ganglion. Fibres relay in the ganglion → post-ganglionic fibres along zygomatic branch of maxillary nerve → zygomatic temporal branch and finally these fibres communicating through lacrimal branch of ophthalmic division to lacrimal gland[1,3].

Salivary reflex

Stimulus generated from the mouth and anterior 1/3rd of tongue → lingual branch of mandibular division of trigeminal nerve (somatosensory) to pons → stimulus is processed in the superior salivary nucleus in pons → pre-ganglionic parasympathetic fibres passes along nervus intermedius → in the auditory canal along with facial and vestibular nerve. Fibres pass by the side of the geniculate ganglion and to facial canal along with motor fibres of facial nerve → pre-ganglionic fibres pass through chorda tympani to the submandibular ganglion. In the submandibular ganglion these fibres relay → post-ganglionic secretory fibres → through the lingual nerve and supply to the submandibular and sublingual glands through its branches.

Stimulus generated from the posterior 2/3rd of tongue → sensory fibres (somatic) pass through 9th cranial nerve to brain stem into inferior salivary nucleus → stimulus is processed in the inferior salivary nucleus → the pre-ganglionic parasympathetic fibres pass through 9th cranial nerve → tympanic branch to tympanic plexus → fibres form lesser petrosal nerve to otic ganglion → post-ganglionic secretomotor fibers → to parotid gland by auriculotemporal nerve[1,3].

Nerve injuries

Different type of nerve injuries are described, like neuropraxia (physiological paralysis of conduction), axonotmesis (intrathecal rupture of nerve fibres with intact sheath) and neuromatosis (partial or complete division of nerve fibres and sheaths)[4].

Neuromatosis: During compete division of nerve fibre, in proximal portion of divided axon, there is retrograde degeneration which occurs as high as first node of Ranvier. After an interval of 10 days, the axons begin to sub-divide and produce an excess of end bulbs, which then commence to grow downwards. However, by this time the gap between the divided nerve ends, which was initially filled with blood, has now been replaced by organising clot and fibrous tissue, a sort of impenetrable barrier to the down-growing axons.

In the distal segment, Wallerian degeneration of axon occurs, the cell of sheath of Schwanns proliferates and forms a bulb from which sprouts of Schwann cells grow proximally into the plan of division, drawn by chemotaxis towards the down-growing axons. A few of the axons succeed in entering the distal segment and lead to the regeneration of nerve fibre[4,5].

In neuromatosis, a well-known phenomenon, mixing of fibres, i.e., mal-distributions of fibres is greatest especially in case of mixed nerves (motor and sensory) or when two or more than two types of fibres are divided and recover together[4].

In this reported case, during head injury, i.e., fracture of base of skull with bleeding from left ear, both pre-ganglionic secretory parasympathetic fibres for salivation and lacrimation of left side must have crushed and completely divided, sparing other nerves and vessels (nervous intermedius – motor part of facial and vestibular nerve) in petrous part of left temporal bone. During recovery of these divided nerve fibres, due to mal-distribution, i.e., some of the secretomotor proximal pre-ganglionic fibres of salivation may have entered into the distal sheaths of pre-ganglionic fibres of lacrimation. This mal-distribution of fibres during recovery can explain these symptoms in this case, i.e., tears (lacrimation) from left eye while eating (salivation).

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CASE REPORT

JIACM 2015; 16(1): 85-6

Pulmonary mucormycosis successfully treated with medical therapy in a diabetic patient

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Abstract

Mucormycosis are serious opportunistic fungal infections that are commonly seen in immunocompromised patients. Here, we present an unusual case of a diabetic patient who presented with cough, shortness of breath for 15 days. On investigation, the patient was diagnosed with pulmonary mucormycosis. Timely diagnosis followed by medical therapy with intravenous liposomal amphotericin B, along with proper management of diabetes by insulin, lead to rapid clinical improvement. The patient was successfully treated without the need of surgical intervention.

Introduction

Mucormycosis is the name given to several different diseases caused by fungi of the order mucorales. The mucoraceae are ubiquitous fungi that are common inhabitants of decaying matter (bread moulds or decaying vegetables)[1]. It is a rare opportunistic devastating fungal infection, which usually occurs in patients with solid organ transplantation, chronic renal failure, patients with neutropenia, and those with poorly controlled diabetes. The manifestation of mucormycosis can be divided into at least six separate entities: cutaneous, rhino-cerebral, pulmonary, gastrointestinal, central nervous system, and disseminated[2]. Predilection for one of these presentations varies with either the underlying or predisposing condition. For example, patients with diabetes most often develop rhino-cerebral mucormycosis while neutropenic patients with hematological malignancy mostly develop pulmonary mucormycosis[3]. Disseminated mucormycosis mostly occurs in patients with bone marrow transplants and acute leukaemia.

Diagnosis is established by histopathological examination of involved tissue and is more sensitive than fungal cultures. This relatively rare, but often fatal disease should be suspected in immunocompromised patients who fail to respond to antibacterial therapy. Early recognition and aggressive management are warranted to maximise cure rates. Optimum therapy requires systemic antifungal therapy, surgical resection, coupled with control of the underlying disease.

Case report

Our patient, a 45-year-old female, a known case of diabetes mellitus, presented with uncontrolled blood sugar and history of cough with sputum and shortness of breath for 15 days and occasional haemoptysis for 3 days. The patient had history of diabetes mellitus since the last 4 years and was on an oral antidiabetic drug. There was no past history of tuberculosis and hypertension and no history of any other chronic illness. No signs and symptoms of rhino-cerebral involvement were present.

On examination, her blood pressure was 126/80 mmHg, while pulse rate and heart rate were normal. On examination of the respiratory system, crackles were present in the left suprascapular, interscapular area, and left infraclavicular and mammary area. Chest X-ray showed an ill-defined, non-homogeneous opacification in the left, upper and mid zone. Haemogram revealed that haemoglobin was 12.8 gm/dl; total leukocyte count was 5,800 mm^3. Erythrocyte sedimentation rate was 52 mm in the first hour. Random blood sugar was 420 mg/dl. Urine ketone bodies were negative. Kidney function tests and serum electrolytes were within normal limits. The patient was non-reactive for HIV-1and 2. Sputum culture and smear for AFB were negative.

The patient was initially started on a course of intravenous antibiotics (ceftriaxone and azithromycin). Blood sugar was controlled with insulin. She did not show any significant improvement in her respiratory symptoms. Subsequently, CT chest was done and it showed a large thick-walled cavitatory mass lesion in the superior segment of the left lower lobe. Another thick-walled cavitatory lesion was seen in the apical segment of the right upper lobe. The patient underwent bronchoscopy; and histopathological examination of biopsy specimen revealed broad aseptate hyphae with irregular branching, consistent with mucormycosis. Subsequent culture examination also confirmed mucormycosis.

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The patient was started on liposomal amphotericin B at the dose of 5 mg per kg per day. Therapy was continued for 5 weeks with close monitoring of renal functions and serum electrolytes. Blood sugar was controlled with insulin. Surgical intervention was deferred due to the proximity of the lesion to carina. Hence the patient was managed medically with close observation.

The patient showed improvement in cough and sputum after one week; and symptoms subsided within a few weeks during the course of treatment. A repeat X-ray chest during treatment also showed radiological improvement. The patient was discharged after 5 weeks. During follow-up, patient is symptom-free after 6 months of medical treatment.

Discussion

Mucormycosis is a rare life-threatening opportunistic fungal infection commonly found in patients with neutropenia and diabetes. Mucormycosis seldom occurs in AIDS patients, except in those with neutropenia or additional risk factors[4]. Because of the aerobic nature of fungi, the rhinocerebral form is the most frequent (55%), followed by pulmonary localisation (30%)[5]. Diabetic subjects are predisposed to rhinocerebral location, whereas neutropenic subjects are susceptible to pulmonary or disseminated infections[6].

Pulmonary manifestations vary from a rapidly progressive fulminant pneumonia, chronic necrotising pneumonia, slowly progressive pulmonary infection, endobronchial polypoidal lesion and intracavitary fungal ball[6]. Pulmonary form may also co-exist with rhinocerebral disease.

Usual symptoms in pulmonary form are nonspecific which may include fever, cough, chest pain, haemoptysis, and dyspnoea which progresses rapidly. The disease being rare, clinical and radiographic features being nonspecific, the diagnosis is difficult[7].

Mucormycosis has an extremely high mortality rate ranging from 25 to 80%. While pulmonary mucormycosis has a high mortality to the tune of 65%, it is 96% in those with disseminated disease. The overall mortality rate of pulmonary mucormycosis is 80%, depending on the underlying disease, delay to diagnosis, and extent of the lesion[5]. The common causes of death are fungal sepsis (42%), respiratory insufficiency (27%) and haemoptysis (13%).

Combined medical and surgical treatment is considered optimal. Mortality is lower with combined treatment as compared to medical treatment alone. Optimal therapy requires control of the underlying disease, surgical resection, and systemic antifungal therapy. Antifungal therapy alone is known to be inferior to combined medical and surgical therapy[8]. 4 - 6 weeks of intravenous amphotericin B remains the mainstay of medical therapy. However, a few novel therapeutic options are available. These options include combination therapy using lipid based amphotericin with an echinocandin or with posaconazole, or with all three[7]. In our case, liposomal amphotericin B was used at the dose of 5 mg per kg per day.

In addition to the mainstay treatment, predisposing factors such as neutropenia associated with haematological malignancy should be reversed with the use of colony stimulating factor and withdrawal of cytotoxic chemotherapy.

Medical therapy alone is rarely beneficial though there are a few reports in the literature where antifungal monotherapy has been used successfully. In our case, the pulmonary cavitatory lesion was successfully treated with a 5-weeks course of intravenous, liposomal amphotericin B alone in the dose of 5 mg/ kg/day. It may be because of indolent form of the disease with less tissue necrosis and angioinvasion.

In conclusion, mucormycosis should be considered in non-immunodeficient diabetic patients with acute and subacute lung disease with cavitation, especially when it fails to respond to antibacterial therapy because early diagnosis and aggressive management maximise the chances for cure and to prevent complications. This case is unique because of pulmonary mucormycosis which responded to medical management alone with amphotericin B and thereby we could avoid surgical resection.

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CASE REPORT

JIACM 2015; 16(1): 87-9

Tuberculosis colliquativa cutis (scrofuloderma) in an immunocompetent child: A rare case report

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Abstract

A rare association of miliary tuberculosis with scrofuloderma is reported. Attention is drawn to the diagnostic importance of skin involvement in cases with suspected miliary tuberculosis.

Introduction

TB is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. Miliary tuberculosis (also known as "disseminated tuberculosis[1]","tuberculosis cutis acuta generalisata[1]",and "tuberculosis cutis disseminata[1]" is a form of tuberculosis that is characterised by a wide dissemination into the human body and by the tiny size of the lesions (1 - 5 mm). Its name comes from a distinctive pattern seen on a chest radiograph of many tiny spots distributed throughout the lung fields with the appearance similar to millet seeds – thus the term "miliary" tuberculosis. Miliary TB may infect any number of organs, including the lungs, liver, and spleen[2].

Scrofuloderma (also known as "tuberculosis cutis colliquativa[1]") is a skin condition caused by tuberculous involvement of the skin by direct extension, usually from underlying tuberculous lymphadenitis[3].

Case report

A 15-year-old male was admitted to our medicine emergency with complaints of breathlessness since 15 days, fever and cough with expectoration since 3 months. He also complained of skin lesions since 3 yrs on various sites on body. Skin lesions had started as small reddish papules with slight itching, gradually increasing in size and ultimately breaking down with dirty white discharge. The patient gave a history that some of these ulcerated lesions healed with some indigenous treatment leaving behind scars. His socio-economic condition was poor. On asking, the mother of the patient gave history that his father had been diagnosed as a case of tuberculosis 14 years back for which he took complete treatment (exact duration could not be recalled by her).

On examination, he was thin built and febrile. Bilateral cervical, axillary and inguinal lymphadenopathy was present. On chest examination, bilateral coarse crepts were present. Mild splenomegaly was also present.

Dermatological examination was as follows: Multiple erythematous-to-voilaceous infiltrated dermal to hypodermal plaques located over the right submandibular region, chest , back , upper and lower extremities sparing mucosa, palms, soles, nails in an asymmetric distribution, measurement varying from 1.5 to 3.5 cm in diameter having peripheral friable crust. On removal of crust an ulcerative area was left. Diascopy test was negative.

The lesion present over right submandibular area had serpiginous ulcers with undermined, inverted edges with soft granulation floor, discharging purulent and caseous material.

Haemoglobin was 8 gm% and total and differential white cell counts were 12,600 cmm and P82/L16/F00/M02 respectively. Mantoux test with PPD I TU was negative. Chest X-ray and CECT showed features of miliary mottling throughout both lung fields.

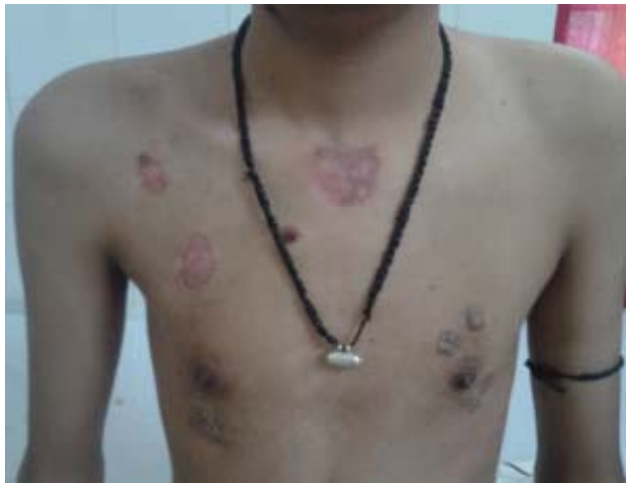

***Fig. 1:** Lesions seen on the chest.*

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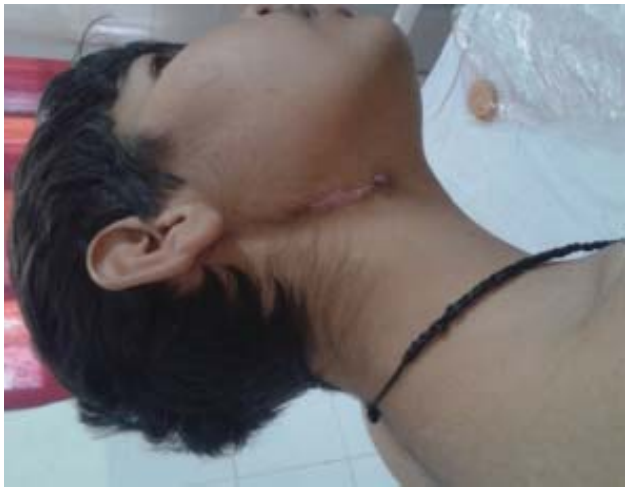

Fig. 2: *Serpiginous ulcer seen over right submandibular area.*

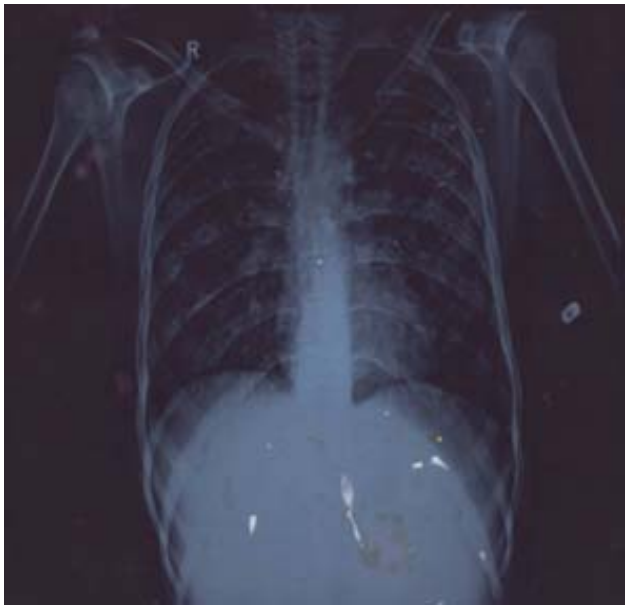

Fig. 3: *Chest X-ray showing miliary mottling.*

His sputum and discharge from ulcers were negative for acid-fast bacilli. HIV status was negative. Biopsy taken from one of the lesions in left forearm revealed destruction of skin with evidence of non-specific abscess formation in the centre. In peripheral portion, tubercular granulomas of varying sizes consisting of caseation, lymphocytes, epithelioid cells and giant cells of Langhans type were seen. The findings were consistent with histopathological diagnosis of scrofuloderma. ATT (category 1) was started and patient showed gradual recovery.

Discussion

TB can involve any organ in the body. Although pulmonary involvement is the most common presentation, extrapulmonary TB is an important clinical problem in

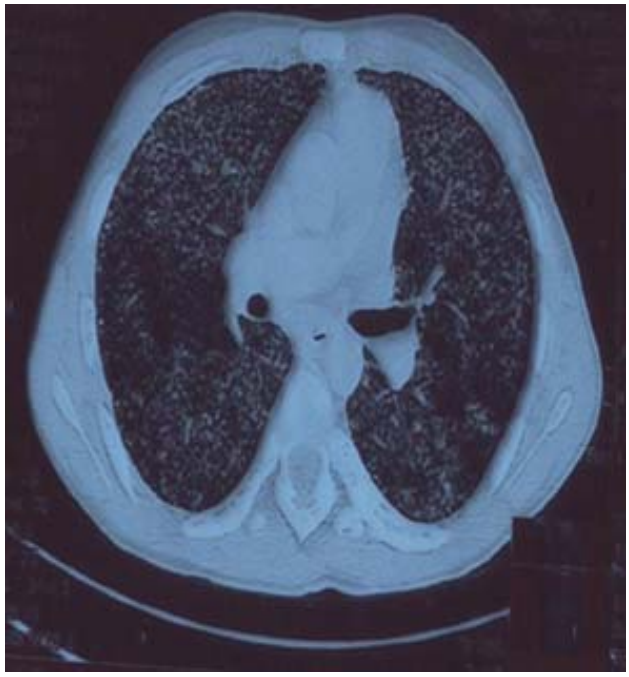

Fig. 4: *CECT showing miliary mottling.*

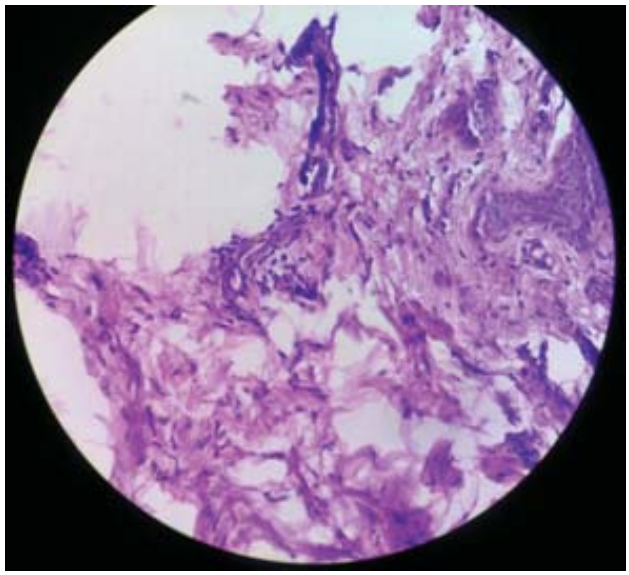

Fig. 5: *HPE showing features suggestive of scrofuloderma.*

daily practice. Disseminated TB refers to involvement of 2 or more non contiguous sites with TB. Dissemination can occur during primary infection or reactivation of a latent focus/re-infection. Miliary TB is an advanced form of disseminated TB. However, according to many authors, miliary and disseminated TB are not different, and the terms are sometimes used interchangeably[4].

In scrofuloderma, the skin lesion usually starts as a bluish red nodule overlying the infected gland or bone and soon breaks down to form undermined ulcers. Progression and

scarring produces irregular adherent masses, densely fibrous in places and fluctuant or discharging in others. Excessive granulation tissue may give rise to fungating tumours[5] (Wilkinson, 1972). Histologically, necrosis and abscess formation found in the centre of the lesion are non-specific. However, the periphery of the abscesses shows tubercular granulomas with caseation necrosis. Tubercle bacilli may, with diligence, be found at the periphery.

The clinical appearance of the skin lesions in our patient was that of scrofuloderma and histological appearances were very suggestive of scrofuloderma. The diagnosis was further confirmed by clinical improvement with specific anti-tubercular therapy. It appears that cutaneous lesions which were now represented by thin atrophic scars, were also of tuberculous aetiology which had healed spontaneously. Spontaneous healing is known in scrofuloderma, though the usual course is a protracted one. Kennedy and Knowles (1975)[6] reported a case of miliary tuberculosis presenting with cutaneous lesions and emphasised that cutaneous abnormalities may not only accompany but may even precede the other evidence of miliary tuberculosis.

Tuberculin test is usually positive both in miliary tuberculosis and cutaneous tuberculosis. However, it may be negative in patients with overwhelming disease. In our patient, who was not critically ill, the negative reaction may have reflected temporary specific anergy to tuberculin as the test became positive subsequently.

Although cutaneous TB is now very rare in developed countries, similar conditions may not exist in our country, and one of the purpose of this report is to emphasise that although cutaneous lesions are rarely encountered in association with miliary TB but when they are found, their diagnostic significance should not be overlooked.

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"The most difficult thing is the decision to act,
the rest is merely tenacity.
You can do anything you decide to do.
You can act to change and control your life;
and the procedure, the process is its own reward."

– Amelia Earhart.

"Walking with a friend in the dark is
better than walking alone in the light."

– Hellen Keller.

CASE REPORT

JIACM 2015; 16(1): 90-2

Nitrofurantoin-induced reversible achromatopsia and visual field constriction defect

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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 grey. There was no history of associated diplopia, cranial nerve palsies, motor weakness, sensory loss, limb incoordination, 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, her 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 P 100 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.

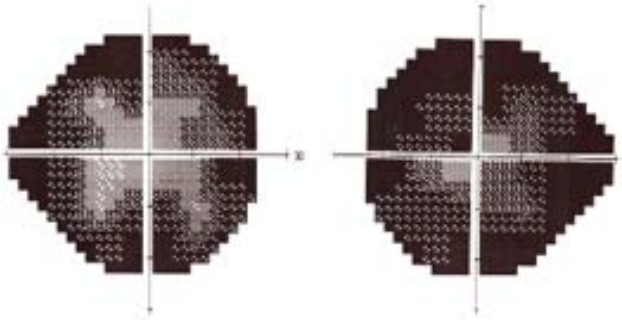

Fig. 1: *Perimetery showing peripheral constriction of visual fields in both eyes.*

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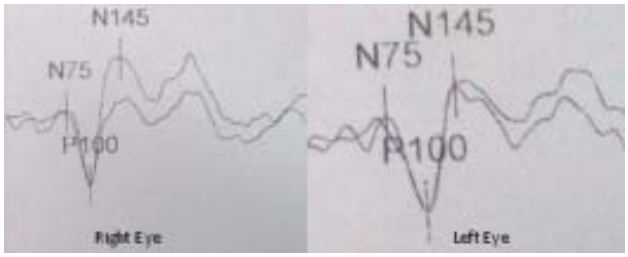

***Fig. 2:** Normal VEP with a P 100 of 101 ms in the left eye and 100 ms in the right eye.*

Discussion

Nitrofurantoin is a synthetic nitrofuran derivative that is used for the prevention and treatment of infections of the urinary tract since 1953[1]. Nitrofurantoin requires the action of intracellular nitrofuran reductase enzymes 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 discolouration of urine. The most common untoward effects are nausea (8%), headache (6%), and rash. 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] 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.

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
Metabolic disorders: Vitamin B_{12} deficiency/diabetes
Inflammatory diseases: Optic neuritis/retrobulbar neuritis/chorioretinal inflammation
Cerebral disorders: Stroke/tumours
Toxins: Tobacco/methyl alcohol/ethyl alcohol/lead/thallium/sulphur-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

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 atrophies. Type III dyschromatopsias are characterised by blue/yellow hue discrimination defects and is 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 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] 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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"Imagination is more important than knowledge."

– Albert Einstein.

"You do ill if you praise, but worse if you censure what you do not understand."

– Leonardo da Vinci.

CASE REPORT

JIACM 2015; 16(1): 93-4

Chavany-Brunhes syndrome – A rare cause of falx cerebri calcification

P Agrawal, V Goyal**, A Agarwal**, VK Rastogi***, A Gupta****, A Goyal******

Abstract

Chavany-brunhes syndrome is a rare cause of falx cerebri calcification. We report a case of a female patient who presented with headache, psychosomatic symptoms and falx cerebri calcification and diagnosed as Chavany-Brunhes syndrome.

Key words: Chavany-Brunhes syndrome, falx cerebri calcification, headache.

Introduction

Falx cerebri calcification is a very rare finding and its causes are many out of which Chavany-Brunhes syndrome is one of them. Chavany-Brunhes syndrome is a rare entity, which can present as headache, psychosomatic symptoms with falx cerebri calcification.

Although Chavany-Brunhes syndrome is implicated as a cause of falx cerebri calcification, online search reported only a few case reports[2]. Here we are reporting a case of Chavany-Brunhes syndrome which presented with headache with falx cerebri calcification.

Case report

A 21-year-old female, housewife, non-smoker, non-alcoholic, presented to our outdoor department with the complaint of recurrent episodes of headache and irritable behaviour for the last 8 - 9 months. The patient also gave history of multiple episodes of unresponsiveness. There was no history of any abnormal body movement or seizure. The headache was mild-to-moderate in severity, diffuse, and continuous in nature. There was no history of nausea and vomiting or blurring of vision, photophobia, lacrimation, redness of eye or early morning headache, or noise intolerance. The patient also gave history of nonspecific generalised bodyache. According to the attendant, the patient had very irritable behaviour, often had quarrel with her husband and in-laws. She became annoyed and angry on small things. She used to beat her children for flimsy reasons. Patient had her menses 9 days back and her menses were regular every 30 days for 2 days. She had no history of fever, cough, cold, decreased appetite, trauma, or ear discharge. There was no history of any medications or ingestion of any toxins. There was no history of anti-tubercular drug intake, hypertension, or diabetes mellitus. On examination, our patient was right-handed. Her vitals were stable with the general examination within normal limits. All systemic examinations (central nervous system, respiratory system, cardiovascular system, abdominal examination) were within normal limits. On investigation, the patient's haemoglobin was: 10 gm/dl; total leukocyte count: 6,800; differentials: N - 70, L - 29, M - 1; urine routine and microscopy, LFT and RFT (including sodium: 136.2 meq/l, potassium: 3.7 meq/l and ionized calcium: 1.15 mmol/l) were normal. Chest X-ray and ultrasound abdomen was normal. Her CT-head showed falx cerebri calcification. Her total calcium was 9.2 mg/dl (8.7 - 10.2 mg/dl), phosphate was 3.4 mg/dl (2.5 - 4.3 mg/dl) and parathyroid hormone was 22 ng/l (8 - 51 ng/l). Her EEG, MRI, and ophthalmic examination were normal. On the basis of headache, psychosomatic symptoms and falx cerebri calcification, she was diagnosed as a case of Chavany-Brunhes syndrome.

Disscusion

Falx cerebi calcification is a very rare finding. It can be physiological or pathological. Pathological causes are endocrine disorders, basal cell nevus syndrome, maroteaux type brachyolmia, hypertelorism and pseudoxanthoma elasticum[7-9]. Miaux *et al*[10] found partial ossification of falx cerebri in two cases out of 13 patients with adult form of myotonic dystrophy[1]. Other causes are Chavany-Brunhes syndrome[2], Gorlin-Goltz syndrome[3]. Chavany-Brunhes syndrome is named after Jacques Brunhes, Jean Alfred Émile Chavany.

Chavany-Brunhes syndrome generally presents with neuropsychiatric symptoms, headache, and falx cerebri calcification. Cause of Chavany-Brunhes syndrome is considered as calcium imbalance. Treatment is based on

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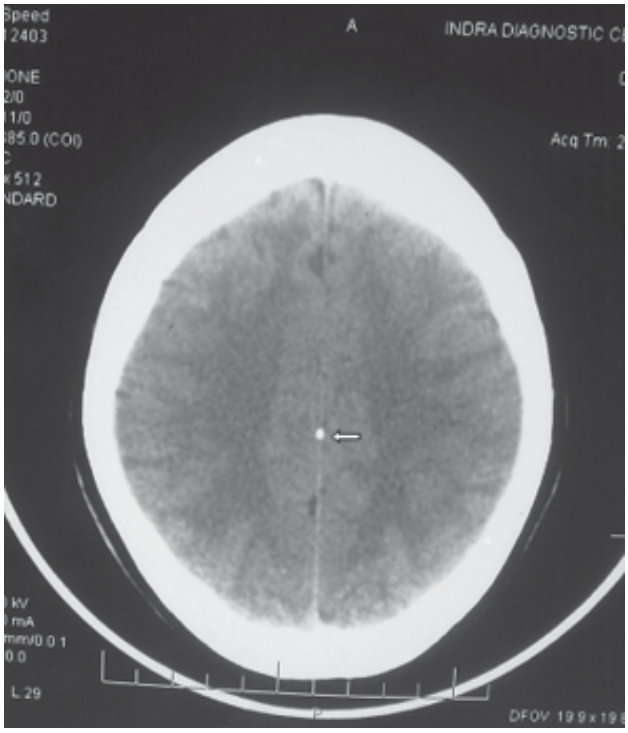

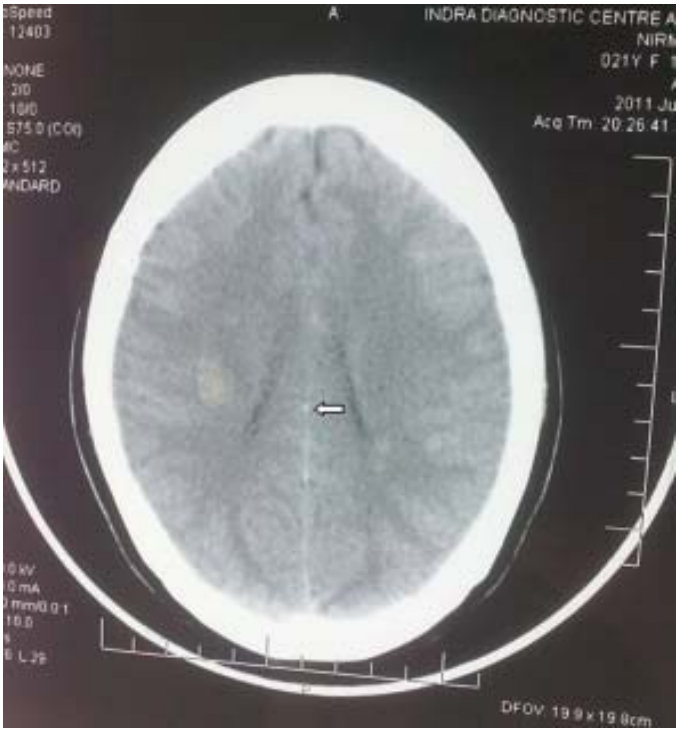

Fig. 1 and 2: *CT scan of head showing falx-cerebri calcification (marked by arrow).*

correction of calcium imbalance, if found, and other symptomatic treatment.

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"What we have done for ourselves alone dies with us;
what we have done for others and the world remains and is immortal."

– Albert Pike.

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Oral and genital ulcers with erythema nodosum

Arun Gogna, Jisa George***

An 18-year-old female with a history of recurrent oral ulcers for one year presented with low-grade fever, genital ulcer, and painful lesions on the shin of both lower limbs of 6 days duration. H/o polyarthralgia was also present. No visual symptoms were present. There was no h/o rashes in any other part of the body. On examination, her vitals were stable. Aphthous ulcer was present on the lower lip (Fig. 1). There were bilateral lower limb deep-seated tender nodules with dusky erythema s/o erythema nodosum (Fig. 2). There was a vulval ulcer on left labia minora (2 X 1 cm) with irregular margins, tender with tiny satellite ulcers tending to coalesce with dirty slough at base (Fig. 3). There was no focal lymphadenopathy. Slit lamp examination of both eyes revealed normal anterior segments. All other systems were within normal limits.

Her haemogram was normal. ESR was 35 mm/hr. CRP was negative. Rest of the metabolic parameters were normal. HBsAg and HIV were negative. Her ANA was negative. Pathergy test was negative. She was detected to have HLA B5/B52 positive. Diagnosis of Behcet's disease was made and she was treated with colchicine 0.5 mg bd and topical ointment for oro-genital ulceration with good healing of the oral and genital ulcer within 2 weeks.

Behcet's disease (BD) is primarily a systemic vasculitis syndrome[1,2]. It is characterised by recurrent episodes of oral and genital ulcers, iritis, and cutaneous lesions. Severe complications include major vessel thrombosis, CNS involvement, and blindness. BD follows a peculiar geographical distribution along the old silk route and there are only a few reports of the disease from northern India – possibly because the disease is either under-diagnosed or under-reported. Pathergy test is positive in about only 49.3% cases as described in the Western literature (ITR-ICBD). These cases occur sporadically[3] and can be detected if the index of suspicion is high.

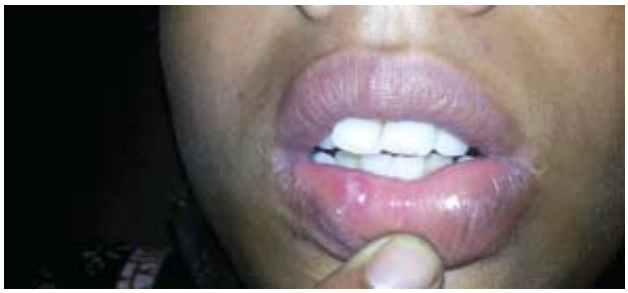

Fig. 1: *Oral aphthous ulcer.*

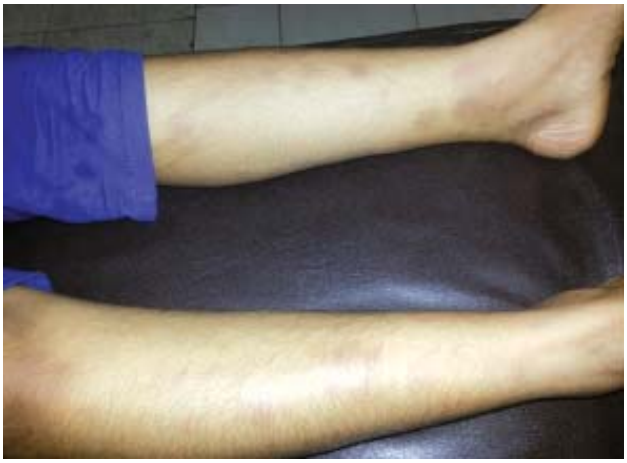

Fig. 2: *Erythema nodosum.*

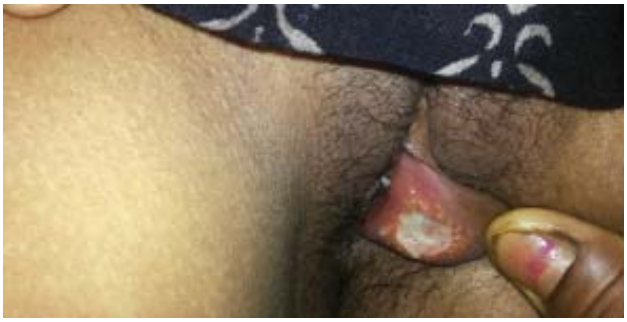

Fig. 3: *Vulval ulcer with tiny satellite ulcers.*

The diagnosis was made according to the ICBD (International Criteria for Behcets Disease) – created in 2006 in replacement to ISG (International Study Group). Getting 3 or more points diagnose/classify as Behcets disease (genital aphthosis 2 points, eye lesions 2 points; skin lesions, oral ulcers and positive pathergy test 1 point each)[4]. Our patient had a score of 4.

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