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Contains 84 pages from 85 to 164 (inclusive of all advertisements)

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VIEW POINT

JIACM 2016; 17(2): 90-91

Quantum world view

*BM Hegde**

"Religion and natural sciences have a point of contact in the issue concerning the existence and nature of a supreme power ruling the world, and here the answers given by them are to a certain degree at least comparable."

– Max Planck (1950).

Science is the biggest enterprise that man ever created. Of all the living things on this planet man is the only one that seems to have started thinking about how this world works. To understand that, he started this new venture, called science, which was originally meant just to understand how this world works. Some exceptionally brilliant minds did accidentally tumble upon some understanding of the world's laws, like gravity, buoyancy, and others in the west while the Indian sages had realised this much earlier. The next step was to find out how the world works by doing some experiments. At this stage the western churches started obstructing their work as this kind of scientific enquiry, they thought, might interfere with the religious belief. That is where the first conflict between religion and science started. The fall out was that the scientists subconsciously developed an aversion to the God concept in religion and thus God was kept out of the scientific realm.

Now that has become a fad and fashion with the young budding scientists to call themselves as atheists. To cap it, a young brilliant mathematical brain of Rene Descartes assumed all power to himself by declaring "Cogito ergo sum" (I think, therefore, I am). If he were a lot more experienced and wise, he would have realised that was his perception and not the world view. There is no perception without a perceiver. In short, we do not have a universe but a multiverse of perceptions, otherwise called the concept of *biocentrism*. Each one of us, including animals, has his or her own perception which is different from others. The world does not run because of that. The real thing should have been "I am, therefore, I am able to think." Let us therefore, think from hereafter.

More and more people started dabbling in science as the world had enough to eat and exist. Finding one's next meal was not that difficult. Science then was more of a hobby for the well-to-do. The leading lights of that generation were Isaac Newton and Albert Einstein. There were a host of others, but less illustrated than the above two, and so are not mentioned here; although some of them like Werner Heisenberg were wiser. Newton's Laws of deterministic predictability and Einstein's laws of relativity together founded a world view of "space-time"constraints where everything else out with this space time module was rejected. They, along with others, tried to split an atom to study the subatomic particles, which in itself was another big business resulting in the atomic bomb! I still remember the words of Max Planck following the bomb blast. "I am proud of my students' cleverness in splitting an atom but am wondering if that atom that they have split might teach mankind a bitter lesson one day which might be too costly for mankind" According to the Space Time world view the speed of light should be the fastest.

When this group had some confusion they would call for a Copenhagen Conference where the problems would be discussed and "settled"! They did not look beyond their noses. They patted each other's back either by their Nobel Prizes or their Fellowships of Newton's Royal Society. Buoyed up by the successful technological advances of their initial scientific laws like the aeroplane, communications' facilities, infrastructure, industrial growth, atom bomb, space travel, weapons of mass destruction, hi-tech medical quick-fixes, etc., scientists also became money wise. Money spoils man. This scientific world view makes man to be arrogant with some scientific authority. They are bound to sell their souls, which in fact, is a sordid boon. They embarked on some funny experiments to split the particles further by colliding them at the speed of light in large submerged reactors at an enormous cost like the CERN scientists looking for the building blocks of this universe. Along with particle physics other natural sciences like chemistry and biology also adopted this reductionist mind set. Evolution was said to be genetic based on Darwin-Mendel hypothesis forgetting the vital role the whole environment plays on evolution, initially put forward by Lamarck. New Evolutionary biologists like Elisabet Sahtouris have tried to revolutionise the field of evolutionary biology where the world view in totally new.

Some thinking physicists started wondering about the behaviour of subatomic particles not confined to the Space time constraints. The particle wave distinction also died down gradually when they could easily discern that both the waves and particles are but the two faces of the same coin. In his article for lay people, Hans Peter Durr, a former Emeritus Director of the Max Planck Institute, wrote "my job was to

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look at matter at its subtlest level and going down the line at one stage I found that there is no matter at all. Was I surprised? – not at all! I expected that!" Starting from Max Planck, de Broglie, Paul Deric, Heisenberg, Schrödinger and many others went ahead with the new ideas and we have now reached a stage where physics took a quantum jump into this new field of quantum physics which has created a new world view which comes closer to reality compared to the old "Space-Time conundrum." For a novice it is a bit confusing as this new world view is more of a possibility than actuality. This comes into view when we look at it and we do not know what happens when we do not look. However, no more doubt remains as most of the new concepts are proven by experimentation. Werner Heisenberg, Niels Bohr, Max Born and Wolfgang Pauli finally resolved the paradox of this "quantum physics" in 1925 with a radical re-interpretation of the dynamics. "It demanded a revolution in what had been the classical view of the world, with the surprising recognition that matter is not really material at all, but a web of relationships, a kind of gestalt, or in a certain way 'information' without any carrier." Hans Peter Durr had a better word in German, the Wirklichkeit.

Experimental physicists have shown that a particle, like in the double slit experiment, could be directed to go through the path that the experimenter wants it to take – mind at work! *Non-locality*, a concept that Albert Einstein did not agree till his last breath, is a reality now. Einstein called it "spooky action at a distance – God playing dice", etc. This reality was a well-known entity in Eastern philosophy, especially Indian Vedanta. *Teleportation*, transfer of knowable or known entity from one place to another without loss of time, and with no communications facilities, has brought spirituality closer to science. When one tries to understand the new quantum physics, one is struck by the existence of a superior intelligence (consciousness) at work in this world. Consciousness has now become a scientific concept and has revolutionised medical science in a big way. That is why I am into this field. Non locality brings in telepathy, a well know concept in Vedanta. Non locality shows that there is the possibility of a particle having its counterpart active at a distance simultaneously. *Quantum entanglement* brings us together. Many other concepts like quantum Tunnelling, etc., take this science nearer to mysticism. Mystics were able to transfer their powers to others. Experiments now have shown how induced brain waves could be simultaneously seen in other brains in contact with the first one psychologically. Are you reminded of telepathy, not an unusual experience in thinkers?

Physics still has to grapple with 95% of dark matter and energy. This is possible with Indian Vedanta. The autobiography of one of the founder fathers of quantum world, Erwin Schrödinger, claimed that he obtained his central intuition from the Vedas. This is a singular credit because without quantum mechanics one cannot understand chemistry, and without chemistry one cannot understand biology and life. Schrödinger and Heisenberg created a universe based on superimposed inseparable waves of probability amplitudes, the sea of waves, and a view consistent with the Vedic concept of All in One." One could argue that the parallels or analogies between Vedanta and quantum theory are merely coincidental. But one can certainly say that Vedanta *did not* follow (plagiarise) quantum logic!

The earlier science gave an impression that man is the one who can make this world run as per the laws of deterministic predictability within the constraints of space time, with speed limited to the speed of light. The Indian concept of *manovega*, the speed of the mind, is a reality in the quantum world. Quantum world view teaches us that we are all the same wave energy and, therefore, interconnected. Once this world view gets currency, all negative human thoughts like hatred, anger, jealousy and greed will have to be replaced by universal compassion making wars and terrorism look foolish and non-productive. When we harm someone else whom are we harming but ourselves? Diseases take a back seat as all of them start in the human mind in negative thoughts. The human mind was confined to the human brain in the earlier world view but quantum world view brings it out in the open as a part of this big universal wave (consciousness). The world can now be compared to the wide sea where we, as individuals, are but a small wave. We ARE a part of that sea. This should make man humble and, consequently, educated. The earlier world view with all its prizes and awards used to make man arrogant and sick. "*But man, proud man, Dress'd in a little brief authority, Most ignorant of what he's most assur'd — His glassy essence — like an angry ape Plays such fantastic tricks before high heaven As makes the angels weep.*" The word "I" used to dominate (starting illness). Now the word is WE (meaning wellness). In the Quantum world view your award is your capacity to be compassionate. This new science opens the flood gates to quantum healing, a limitless field. This also leads to the inner development of man for the good of mankind.

That said, I must hasten to add that there will not be too many to buy this truth as this is not a good business proposition and might not allow us to make money like the reductionist world view of the past. My good friend, Amit Goswami, a bright Bengali professor of Theoretical Physics at the Oregon University, USA is trying his level best to spread the message of quantum physics to the world. He is doubly qualified as he is a scholar in Indian Vedanta as well. My hope is that this scientific truth of quantum reality would bring man and man together *"To Give without Remembering and Receive without Ever Forgetting."*

"I don't argue things being spiritual versus scientific, because I've never met anyone who knows enough about either to be convincing—including myself."

– S. Kelley Harrell.

ORIGINAL ARTICLE

JIACM 2016; 17(2): 92-94

Acute malarial nephropathy – A complication less recognised

Sushma Trikha, Neelima Singh**, Pradeep Prajapati**, Archana Kansal*, Navneet Agrawal****

Abstract

Malaria induced acute renal failure is a complication less well known than anaemia and cerebral malaria, but the mortality in this subgroup is high, especially when the disease is not diagnosed early. It may present as a part of a multi-organ dysfunction, or as a lone complication. This study was aimed to find-out the incidence of acute renal failure in patients with malaria, association with various complications, and the outcome with the management offered in our set-up. Cerebral malaria, anaemia, hepatic involvement, and acute respiratory distress were common in patients with malaria-induced acute renal failure.

Keywords: Acute renal failure, anaemia, cerebral malaria.

Introduction

Malarial acute renal failure (ARF) is emerging as an important problem in tropical countries, and carries a high mortality, especially when the disease is not diagnosed early. Acute renal failure (ARF) is seen mostly in *Plasmodium falciparum* infection, but *P. vivax* and *P. malariae* can occasionally contribute towards renal impairment[1,2,3]. Malarial ARF is commonly found in non-immune adults and older children with falciparum malaria[4,5]. However, recently it has been reported more often in semi-immune African children with associated morbidity and mortality[6]. Several factors including various chemical mediators, catecholamine release, cytoadherence of parasitised erythrocytes, dehydration, intra-vascular haemolysis, intra-vascular coagulation, sepsis, hyperbilirubinaemia, and hyperparasitaemia have been implicated in the pathogenesis of ARF in malaria. Haemodynamic alteration, haematologic change, and immunologic response are among the major pathophysiologic mechanisms in the pathogenesis of the disease. Disturbances in the renal microcirculation are responsible for acute renal failure; massive intravascular haemolysis causes haemoglobinuria with or without renal failure; and immunologic reaction to parasites accounts for glomerular lesions. Risk factors for poor outcome were anaemia, jaundice, cerebral malaria, disseminated intravascular coagulation[7].

Aims and objectives

1. To study the incidence and outcome of acute renal failure in cases of malaria.
2. To study the relation of acute renal failure with various complications of malaria.

This study was conducted with an objective to highlight the occurrence of acute nephropathy in patients with malaria.

Material and methods

Material

This is a prospective study which was conducted over a period of one year from September 2008 to August 2009 in JA Hospital, G. R. Medical College, Gwalior. All patients positive for malarial parasite were included as subjects. Patients with pre-existing renal disease were excluded.

Method

All the patients with confirmed malaria were subjected to a detailed clinical and biochemical examination as per a pre-structured proforma. Patients were grouped into two categories on the basis of renal failure (i.e., those with and these without renal failure). Those patients with acute renal failure were grouped into three categories on the basis of RIFLE Criteria. RIFLE defines 3 grades of increasing severity of ARF on the basis of change in serum creatinine: R – risk (serum creatinine 1.5 times the normal), I – injury (serum creatinine 2 times the normal), F – failure serum creatinine 3 times the normal); and 2 outcome variables: L – loss, E – end-stage kidney disease. Patients with established end-stage renal kidney disease and chronic kidney disease on maintenance dialysis were excluded from the study. Clinical profile and biochemical profile of patients with acute renal failure was studied. The mangement included appropriate anti-malarial, fluids, electrolytes, and dialysis if indicated. Data was analysed to find-out the incidence of acute renal failure in malaria, and the outcome. The association between various complications and acute renal failure was assessed using univariate analysis, odd ratio.

Results

A total number of 1,145 patients positive for malarial parasite were enrolled as subjects. Females (53.53%) out-numbered

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males (46.46%). Most of the patients (51.87%) were in the age group 21 - 40 years. Falciparum malaria was found to be positive in 607 (53.01%) patients, vivax malaria in 497 (43.40%), and mixed infections (falciparum and vivax) in 41 (3.59%) patients.

83 (7.24%) patients developed acute renal failure. Out of 83 patients with ARF,47 (56.6%) were males, and 36 (43.3%) females. 41 (49.39%) patients were in the age group 21 - 40 years. 67 (11.03%),10 (2.01%), and 6 (14.63%) patients with falciparum malaria, vivax malaria, and mixed malaria respectively developed acute renal failure.

Clinical profile of patients with acute renal failure was as follows: fever - 77 (92.77%), altered sensorium - 27 (32.5%), oedema - 39 (46.98%), dyspnoea - 23 (27.71%), diarrhoea - 7 (8.43%), pain abdomen - 4 (4.81%), convulsions - 2 (2.40%), pallor - 32 (38.55%), icterus - 30 (36.14%), hepatomegaly - 33 (39.75%), and splenomegaly in 31 (37.34%).

Significant biochemical profile in patients with acute renal failure revealed anaemia in 31 (37.3%), hyponatraemia in 30 (35.7%), hyperkalaemia in 5 (5.9%), hyperbilirubinaemia in 33 (39.3%), and elevated liver enzymes in 30 (35.7%) patients.

Urinalysis in patients of malarial ARF showed microscopic haematuria in 10 (11.9%), granular casts in 24 (28.57%), and albumin in 38 (45.23%).

On the basis of RIFLE criteria, patients were divided into 3 groups. Those at risk were only 6 (7.22%) cases with falciparum malaria; those with acute kidney injury (AKI) were 19 (22.6%) patients with falciparum malaria, 7 (8.33%) with vivax malaria, and 3 (3.57%) with mixed malaria; and those with acute renal failure were 40 (47.6%) with falciparum malaria, 5 (5.95%) vivax malaria, and 3 (3.57%) with mixed malaria. Non-oliguric acute renal failure was observed in 19 (20.23%) patients. All the 14 (16.86%) patients who expired were those with ARF. None in the risk category or with acute kidney injury succumbed to malaria.

58 (69.87%) patients were managed conservatively while 25 (30.12%) required dialysis. Out of 25 patients who were dialysed, 22 (88%) improved; and 3 (12%) patients expired. Associated complications of malaria in patients with ARF were anaemia in 31 (37.3%), hepatic involvement (raised serum bilirubin, and elevated liver enzymes) in 37 (39.2%), cerebral malaria in 23 (27.38%), and acute respiratory distress in 2 (4.76%) patients. Univariate analysis showed significant association of various complications of malaria with ARF (Table II). Univariate analysis Odd ratio for cerebral malaria 1.74 (1.06 – 2.22) p value - 0 .00001, anaemia 0.59 (0.37 - 0.93) p value - 0 .0003, hepatic involvement 7.82 (4.84 - 12.64) p value 0.00016, ARDS 6.53 (1.18 - 36.20) p value 0 .00001.

Overall mortality was 78 (6.8%). Mortality was 64 (6.02%) in those without acute renal failure, and 14 (16.86%) in those with acute renal failure.

Table I: Showing severity of acute renal failure in different types of malaria.

		(n = 83)		
S. No	**Severity of ARF**	**Falciparum malaria**	**Vivax malaria**	**Mixed malaria**
1.	At risk (n = 6)	6 (7.22%)	0	0
2.	Acute kidney injury (n = 29)	19 (22.89%)	7 (8.43%)	3 (3.61%)
3.	Acute renal failure (n = 48)	40 (48.1%)	5 (6.02%)	3 (3.61%)

Table II: Association between various complications of malaria in patients with and without acute renal failure.

S. No	Complications	With ARF 83 cases	Without ARF 1,062 cases	Univariate Analysis Odd ratio	p value < 0.05 significant
1.	Cerebral malaria	23 (27.38%)	192 (17.96%)	1.74 (1.06 - 2.22)	0.00001
2.	Anaemia	31 (37.3%)	535 (50.04%)	0.59 (.37 - 0.93)	0.0003
3.	Hepatic involvement	37 (39.2%)	99 (9.26%)	7.82 (4.84 - 12.64)	0.00016
4.	Acute respiratory distress syndrome	2 (4.76%)	4 (.37%)	6.53 (1.18 - 36.20)	0.00001

Discussion

83 (7.24%) patients developed acute renal failure. Overall mortality in malaria was 78 (6.8%). Comparing patients with renal failure and those without, mortality was (16.86% vs 6.02%).

67 (11.03%), 10 (2.01%), and 6 (14.63%) patients with falciparum malaria, vivax malaria, and mixed malaria respectively developed acute renal failure (Table I). Out of 14 patients with ARF who expired 12 patients had *P. falciparum* and 2 patients had *P. vivax*. This means that the benign tertian malaria is not always benign. *P. vivax* malaria has the propensity to cause ARF, which occurs more commonly in *P. falciparum* malaria[1,2,3]. Renal involvement varies from mild proteinuria, haematuria, to severe azotaemia.

Acute nephropathy (ARF/AKI) may present as a component of multi-organ dysfunction (MOD), or as a lone complication. In this study, complications like cerebral malaria, anaemia, hepatic involvement, acute respiratory

distress syndrome (ARDS) emerged as an important association in simple univariate analysis in those with acute renal failure (Table II). These associations may have a role to play in prognosticating the outcome. Cerebral malaria was seen in 23 (27.38%) patients, and 31 (37.3%), 37 (39.2%), 2 (4.76%) had anaemia, hepatic, and respiratory involvement. ARF necessitating dialysis was seen in 25 (30.12%) cases. 69 (83.1%) patients with ARF recovered, and 14 (16.86%) patients expired. Associated complications might have contributed to mortality. Low haemoglobin, hyperbilirubinaemia, cerebral malaria, and high serum creatinine were the main predictors of mortality[7].

Immunity to malaria usually requires repeated exposure to the parasite to become long lasting. One reason for this is the capacity of the parasite to vary the antigens which are major targets for protective antibodies[8].

Jaundice was found to be present in 37 (39.2%) patients with ARF, and 99 (9.26%) patients without ARF (p value = .00016). It may have both unconjugated component resulting from the excessive haemolysis and a conjugated element resulting from cholestasis. The presentation of jaundice associated with malaria needs to be recognised as delayed diagnosis and inappropriate treatment may lead to increased mortality[9].

Volume depletion, hyperbilirubinaemia, intra-vascular haemolysis and sepsis are responsible for ARF. Hyponatraemia was present in 30 (35.7%) patients with acute renal failure. The precise pathophysiological mechanisms of hyponatraemia in malaria requires further study[10].

Presence of acute renal failure and jaundice together adversely influences the mortality. Non-oliguric renal failure usually has better prognosis[11].

Untreated or delayed treatment may have adverse effect on cerebral, renal, and hepatic functions, and therefore prompt intervention is essential in complicated cases of malaria. Currently, a standard intensive care, avoidance of nephrotoxic drugs, early institution of renal replacement therapy, appropriate antimalarials, and supportive management can reduce morality, and enhance recovery of renal function[12].

Conclusion

Incidence of malarial ARF was 7.24% in this study. Renal failure in malaria appears to be a complication less well known. Complications like cerebral malaria, anaemia, hepatic involvement, acute respiratory distress syndrome are common in patients with malarial ARF. The presentation of renal failure associated with malaria needs to be recognised globally in order to reduce mortality.

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"The Earth has rights too, to live without pollution.
What mankind must know is that human beings cannot live without Mother Earth,
but the planet can live without humans."

– Evo Morales.

ORIGINAL ARTICLE

JIACM 2016; 17(2): 95-98

Profile of medical illness, hypertension, diabetes mellitus, cerebrovascular accident, chronic renal failure, and coronary artery disease in patients attending a geriatric OPD

YK Gupta, HS Bhardwaj**, BL Bhardwaj***, H Singh****, S Aggarwal*****, GK Bedi*******

Abstract

The elderly population is increasing rapidly globally, and presently, India has the second largest number of elderly persons. The population of the elderly has shown an increase from just 5.6 per cent in 1961 to 7.7 per cent in 2001. This has resulted in an increase in the burden of diseases in the elderly due to various physical and mental ailments.

Aims of the study: To study the profile of medical illness, hypertension, diabetes mellitus, cerebrovascular disease, chronic renal failure, and coronary artery disease in the elderly patients and in relation to gender in patients attending the geriatric out-patient department of Rajindra Hospital, Patiala.

The study was conducted in the geriatric out-patient department of Rajindra Hospital, Patiala, and a total of 500 consecutive patients, aged 60 years and above were enrolled. The data from these patients was collected by a detailed history and physical examination as per the pre-designed proforma. The relevant investigations were done, wherever needed.

Results: The mean age of our patients was 69.78% in males, and 68.76% in females. The prevalence of various medical disorders in our study was hypertension – 40% (males 38.9%, and females 42.16%), coronary artery disease – 39.6% (males 37.12%, and females 44.5%), diabetes mellitus – 17% (males 16.76%, and females 17.46%), stroke – 6% (males 6.2%, and females 5.4%), and chronic kidney disease – 5% (males 5.08%, and females 4.82%).

Conclusion: The study shows high prevalence of hypertension, diabetes, coronary artery disease, in the elderly persons coming to geriatric OPDs.

Key words: Old age, hypertension, diabetes, coronary artery disease.

Introduction

At the beginning of this century, 12 million Indians were aged 60 years or more. The number of aged doubled in the next sixty years in 1961 to 24 million, and since then there has been a great rise in the number to 56 million in the year 1991, and 70 million in 2001. The projected figure for the year 2016 is 112 million. The decadal growth rates in > 60 age group since 1951 - 1961 have remained above 26% and are about 5% to 8% higher than that for the total population. There has also been tremendous increase in life expectancy at birth and at 60 years of age. Expectancy of life at birth has shown a rise of more than 10 years from 49.7 years during 1970 - 1975 to 60.3 years during the period 1991 - 1995. Over this quarter century, expectancy of life at 60 and 70 years has also shown significant rise from 13.8 and 8.9 years respectively to 16.2 and 10.6 years[1]. With further improving living standards, comes better health and easy access to medical services, leading to a decline in mortality rates and higher life expectancy. According to the UN estimates, during the period 1995 - 2000 in India, the life expectancy of males stood at 62.3 years while that of females was 62.9 years. For the period 2020 - 25, the projected figures are 68.8 years for males and 72.1 years for females and for the period 2045 - 50 the estimates are 73 years for males and 76.9 years for females. All over the world, the elderly population is growing continuously and it is projected that by the year 2025, majority of the elderly people worldwide will be residing in developing countries[2]. India is amidst a demographic transition with a trend towards an ageing population[3]. In India, the ageing population above 60 years has been estimated to almost double-up from 7.7% in 2001 to 12.30% in 2025 and the number of elderly people will be nearly 150 million[4-5].

Hence, the present study was undertaken to know the pattern of various common diseases for which elderly patients seek medical attention in the geriatric outdoor-patient in the setting of Rajindra Hospital, Patiala.

Material and methods

The study was conducted in the geriatric OPD of Rajindra

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Hospital, Patiala. A total of 500 patients aged 60 years and above from either sex were enrolled and data from these patients was collected in the form of a detailed history and physical examination as per the pre-designed proforma. The relevant investigations were undertaken in all the patients, wherever needed. The diagnosis of various diseases was made as per the standard disease definitions corroborated with the relevant investigations. Hypertension was diagnosed according to JNC VII guidelines. Coronary artery disease was diagnosed by history, electrocardiogram, and CPK-MB levels.

Patients were labelled diabetic, if they fulfilled the ADA criteria on blood sugar levels. Chronic kidney disease was diagnosed as per National Kidney Foundation - K/DOQI guidelines when patients had evidence of structural renal disease on ultrasonography and/or deranged kidney function tests. Stroke was confirmed by CNS imaging (CT scan). The data collected was analysed and the results were obtained as the percentage of total elderly patients for various diseases.

Results

For convenience, geriatric patients were further divided into 3 groups of 60 - 70 age group having patients whose age was less than 70 years but more than 60 years. Patients of age 70 years and more, but less than 80 years, were grouped in the second group and patients of age 80 years and above were be taken in third group. Distribution of patients according to age and sex is shown in Fig. 1.

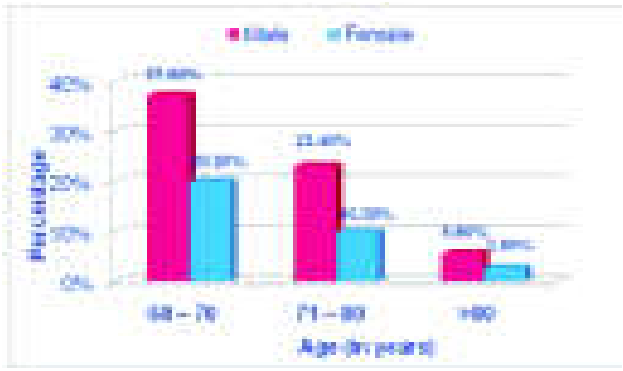

Fig. 1: *Correlation of baseline ERI with baseline hsCRP levels.*

Hypertension

In the present study the total number of hypertensive male patients were 130 and hypertensive females were 70. Therefore there were a total 200 patients of hypertension. Percentage of hypertension cases according to age and sex distribution is shown in Table I.

Table I: Percentage of hypertension cases according to age and sex distribution.

Age group (in years)	Male n = 334		Female n = 166	
	No. of cases	% age	No. of cases	% age
60 - 70	62	18.56	42	25.30
71 - 80	55	16.46	19	11.44
> 80	13	3.89	9	5.42
Total	130	38.91	70	42.16

Overall prevalence of hypertension in population = 200/500 x 100 = 40%.

Diabetes

In the present study there were 58 diabetic males and 27 diabetic females. There were therefore 85 diabetic patients. So the overall prevalence of diabetes in the present study was 17%. Age and sex distribution is shown in Table II.

Table II: Number of cases found to be diabetic.

Age group (in years)	Male (% age)	Female (% age)
60 - 70	10 (2.99)	6 (3.61)
70 - 80	28 (8.39)	12 (7.23)
> 80	20 (5.99)	9 (5.42)
Total	58 (17.37)	27 (16.26)

So the overall prevalence of diabetes was found to be 85/500 x 100 = 17%.

Stroke

In the present study the total number of males suffering stroke were 21 and females suffering from stroke were 9. Therefore, there were total 30 patients of stroke. Age and sex distribution is shown in Table III.

Table III: Cases having stroke/CVA.

Age group in years)	Male		Female	
	Total no. of patients (% age)	Patients of CVA (% age)	Total no. of patients (% age)	Patients of CVA (% age)
60 - 70	188 (37.60)	10 (2.99)	101 (20.20)	4 (2.41)
71 - 80	117 (23.40)	9 (2.69)	51 (10.20)	3 (1.81)
> 80	29 (5.80)	2 (0.60)	14 (2.80)	2 (1.20)
Total	334 (66.80)	21 (6.28)	166 (33.20)	9 (5.42)

The overall prevalence of stroke was 30/500 x 100 = 6%.

Chronic renal failure (CRF)

In the present study the total number of males having CRF were 17 and females having CRF were 8. Therefore, there were a total of 25 CRF patients. Age and sex distribution is shown in Table IV.

Table IV: CRF cases on basis of abnormal s. urea/ s. creatinine/ultrasound reports.

Age group (in years)	Male (n=334)		Female (n = 166)	
	Total no. of patients (%age)	Patients of CRF (%age)	Total no. of patients (%age)	Patients of CRF (%age)
60 - 70	188 (37.60)	7 (2.09)	101 (20.20)	5 (3.01)
71 - 80	117 (23.40)	7 (2.09)	51 (10.20)	2 (1.20)
> 80	29 (5.80)	3 (0.90)	14 (2.80)	1 (0.60)
Total	334 (66.80)	17 (5.08)	166 (33.20)	8 (4.81)

Therefore the overall prevalence of CRF = 25/500 x 100 =5%.

Coronary artery disease (CAD)

In the present study the total number of male patients having CAD were 124 and females suffering from CAD were 74. So there were a total 198 CAD patients. Percentage of cases according to age and sex is shown in Table V.

Table V: CAD cases.

Age group (in years)	Male		Female	
	Total no. of patients (% age)	Patients of CAD (% age)	Total no. of patients (% age)	Patients of CAD (% age)
60 - 70	188 (37.60)	71 (21.26)	101 (20.20)	45 (27.10)
71 - 80	117 (23.40)	42 (12.58)	51 (10.20)	23 (13.86)
> 80	29 (5.80)	11 (3.29)	14 (2.80)	6 (3.61)
Total	334 (66.80)	124 (37.12)	166 (33.20)	74 (44.57)

The overall prevalence of CAD = 198/500 x 100 = 39.5%.

Discussion

Well being of older person has been mandated in article 41 of constitution of India which directs that state shall within the limits of its economic capacity and development make effective provision for securing the right to public assistance in case of old age.

Of the 3 groups, we find most of our cases clustered in the 60 - 70 years age group (57.4%), in concordance with the demographic profile of India. In the terms of health status, the difference between the males and females are clearly explicated as females have higher rate of morbidity. In the process of caring and nurturing of other members of the family, women in India, invariably tend to neglect or overlook their own well being.

In the present study, hypertension was the primary diagnosis in 40% of the elderly patients attending geriatric OPD, most common being in the 60 - 70 years age group. This is almost equal to 39.5% prevalence found by Kalra *et al*[6]. A study done by Puria *et al*[7] also showed similar results (41.9%). Experiences from geriatric clinics in Northern India revealed that hypertension was the most commonly reported physical diagnosis (50%)[8]. The Udaipur study noted that in the morbidity profile of old age, hypertension is present in 48% of subjects[9].

Hypertension is a powerful, independent, and modifiable risk factor for the development of all the major clinical manifestations of atherosclerotic cardiovascular disease that commonly affects the elderly including CAD, stroke, peripheral vascular disease, heart failure, renal failure, and dementia. Our study also showed hypertension showing female predominance being prevalent in 41.5% as compared to 39.2% in males. Studies done by various other researchers like Leena *et al*[10], and Kakkar *et al*[11] also showed female predominance.

Diabetes was the reason for consulting a physician in 17% of the elderly attending the geriatric OPD. India is the diabetic capital of world. Eun-kyung Woo *et al* reported a prevalence of 14.9% diabetes mellitus in the people of South Korea[12]. The prevalence in our study is similar to that found by Kalra *et al*[6]. While Kakkar *et al*[11] found the prevalence to be 32% in the geriatric population in Delhi – could be because it was a house to house survey, while our study was based on only those who attend OPDs, as in our community people take a long time to visit a doctor because of various reasons. Also diabetes was found more in females than males. Various studies support this, e.g., Kakkar *et al*[11], Bharati *et al*[13], and Swami *et al*[14].

Reliable morbidity and mortality estimates for stroke in India are limited due to incomplete death certification, incorrect death classification, and uncertainity of aetiology in cases of sudden death or multiple co-morbitities. As our study was based only on OPD patients, it included only those who were follow-up cases, because stroke is an acute condition which needs emergency treatment. Those who died or were referred to higher centres generally did not come for follow-up. The present study suggested the prevalence of stroke to be 6%. This is almost comparable to a study done by Kalra *et al*[6]. We also observed a significant gender difference in stroke prevalence, which is all the more important when we consider that this study looked

at only the geriatric group, when the endothelio-protective effects of female sex hormones would have waned. One possible explanation for this difference may be the higher rates of tobacco smoking and alcohol use in men, compared to women. Male prevalence was also found to be more in various studies like Huang *et al*[15] and Banerjee *et al*[16].

About 1,10,000 patients in the United States started treatment for ESRD in 2007. Leading causes of ESRD are diabetes and hypertension. In 2006, 7 out of 10 new cases of ESRD in the United States had diabetes or hypertension listed as the primary cause. Our study showed the prevalence of CRF as 5% which is close to 4.5% shown by Kalra *et al*[6]. CRF is quite an important aspect, as once CRF develops, very few percentage of cases go for its final treatment, i.e., renal transplant because of various reasons. The present study also showed that there is not much difference in the prevalence of CRF between males and females. The study done by Jungers *et al*[17] also stated this.

CAD was found to be the second most common disease in our study, accounting 39.6%. The results of our study are found similar to study done by Shabbir *et al*[18]. It has been estimated that approximately one quarter of all deaths in developing countries and almost half of all deaths in developed countries are attributable to cardiovascular diseases[19].

CAD is highly prevalent in the elderly because of the high prevalence of various risk factors and morbidities at this age, e.g., hypertension, diabetes mellitus, obesity. Age itself is a risk factor for CAD. Also CAD increases with age. Regarding this also, the results of our study match with the study of Shabbir *et al*[19]. CAD like hypertension, diabetes mellitus was more prevalent in females in our study – being 37.2% in males and 45% in females. Shabbir *et al*[19] also say this.

Actually hypertension, cardiovascular diseases, cerebrovascular accident, diabetes mellitus and obesity are under the same umbrella of modern non communicable diseases.

Conclusion

The present study showed a high prevalence of hypertension, coronary artery disease and diabetes in the elderly persons attending the medical out-patient department in a tertiary care hospital in Patiala. However, larger studies are required to elucidate the exact magnitude of the problem.

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ORIGINAL ARTICLE

JIACM 2016; 17(2): 99-101

Role of cardiac biomarkers in assessing risk in chronic kidney disease

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Abstract

Aim: To find out whether assessment of blood levels of troponin I and cardiac enzymes can be utilised to detect high-risk cases of chronic kidney disease (CKD).

Materials and methods: 109 patients diagnosed to have CKD who were undergoing dialysis or attending the OP of the department of nephrology were studied. Blood levels of different cardiac biomarkers were estimated for all the patients. Patients were staged by calculating eGFR. Correlation between the cardiac biomarker levels and stages of CKD was done statistically.

Results: Statistically significant correlation existed between stage of kidney disease and troponin I levels (R value -0.1.5).

Conclusion: Estimation of cardiac markers to assess the cardiac status of CKD patients will be beneficial in detecting patients having cardiac problems complicating CKD.

Introduction

There has been an increase end-stage renal disease (ESRD) patients all over the world[1]. Among the CKD population, CAD is highly prevalent. Prevalence has been estimated to vary from 15% to 73%. The wide range in prevalence is mostly because many cardiac disease cases present asymptomatically. It is estimated that > 50% of patients – particularly diabetics – are asymptomatic[2].

Cardiac disease is also the major cause of death in patients with ESRD, accounting for about 45% of all deaths[3]. There has been a dramatic 40-fold increase in death rates among dialysis patients, as compared to the general population as was first reported by Sarnak and Levey[5]. This appears to be associated with the heavy burden of cardiovascular disease (CVD) among patients with ESRD[6]. The prevalence of CVD at initiation of dialysis also has increased dramatically from 25% in 1984 to 40% by 1999, in United States[7]. But, despite advances in chronic heart failure treatment, the prognosis of these patients remains poor[8].

Even though many studies show the importance of renal function tests and other biochemical parameters in assessing prognosis in CKD patients, less emphasis has been placed on biomarkers of cardiac function. Hence a study to assess the relationship between cardiac biomarker levels in blood and renal function will help in diagnosing the high-risk group among CKD patients. This will also help to divert resources to the more needed group of patients in the society as CKD is becoming a very common public health problem especially among the elderly.

Material and methods

109 patients, including 32 (38.5%) females and 87 (61.5%) males were studied. Mean value of the different parameters studied are given in Table I.

Table I: Mean values of the parameters studied.

	Mean	Studied deviation
Age	45.69 years + SD	13.76
Urea	96.04 mg%	35.1, g%
Creatinine	7 mg%	3.6 mg%
AST	38.67 U/L	23.74 U/L
CK-MB	11.831 U/L	14.28 IU/L
Troponin 1	5.24 ng/ml	13.02 ng/ml

After calculating eGFR from serum creatinine level using MDRD formula, patients were staged. Patients belonged to stages II, III, IV and V. There were no patients of stage I. Distribution of patients is as follows: stage V – n - 80, stage IV – n - 11, stage III – n - 14, stage II – n - 4 and stage I – n - 0.

Among cardiac biomarkers tested, means of AST and CK MB levels were within normal limits (mean AST – 38.67U/ml, CK MB - 11.831 U/ml). Mean troponin-I level was found to be high – 5.24 ng/ml.

Stagewise distribution of blood levels of the different parameters is given in Table II.

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Table II: Stagewise distribution of blood levels of the different parameters.

		N	Studied deviation	P value
Trioponin I	Stage II	4	.042	
	III	14	.492	
	IV	11	9.82	
	V	80	14.57	
	Total	109	13.02	0.329
AST	Stage II	4	1.59	
	III	14	32.07	
	IV	11	22.32	
	V	80	22.54	
	Total	109	23.74	0.175
CK-MB	Stage II	4	10.5	
	III	14	15.28	
	IV	11	10.29	
	V	80	14.16	
	Total	109	14.28	.024

Among the different parameters tested, the mean troponin I level increased with higher stages. Stage II - 0.043 ng/ml, stage III - 0.198 ng/ml, stage IV - 4.64 ng/ml, and stage V - 6.46 ng/ml. Mean AST level was not found to increase with stage of disease. Highest mean AST level was seen in stage IV. Similarly in the case of CK-MB also, highest mean value was found in stage III.

Levels of these cardiac biomarkers were compared between the 4 stages of kidney disease by ANOVA using SPSS version 16 (Table III).

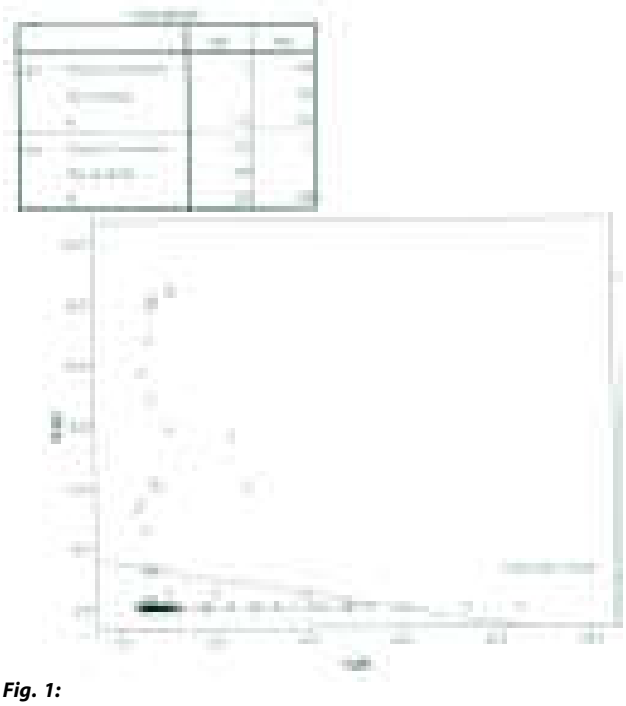

Fig. 1:

Table III: Comparison of markers between different stages using ANOVA.

	Significance
Troponin I	.329
AST	.175
CK-MB	.024

CK MB values showed significant variation between the 4 stages (p - .024). The mean of each of these parameters in each stage was compared with the means in other stages using Bonferroni method also. This also showed statistically significant results in the case of CK-MB. At the same time, variation in troponin I, and AST values between the 4 stages was not significant statistically.

Correlation of troponin I, CK MB, and AST with eGFR which is indicative of stage of kidney disease was done by Pearson correlation. Correlation was found to exist between eGFR and troponin I level but it was not found to be statistically significant.

Discussion

Recent publications show an increase in the extent of CKD in the general population[9]. There are reports on the increasing burden of CVD associated with the CKD population also[10]. In fact, 5 - 10 times higher rate of death has been documented among CKD patients which is assumed to be because of CVD[5]. Among cardiac diseases, ischaemic heart disease (39%), congestive heart failure (41%), arrhythmia (31%), and other heart diseases (63%) have also been documented to be on the rise among CKD patients in various reports[5,11]. Chronic kidney disease patients showed a 5-times higher rate of hospitalisation for congestive heart failure, greater than that of non-CKD patients[5]. These point to the fact that monitoring for markers of ischaemic heart disease is not sufficient to identify the high-risk group among CKD patients.

Estimation of B-type natriuretic peptide measurement (BNP and NT-proBNP) can be done for the diagnosis of acute decompensated HF[12]. To reduce cardiovascular complications in diabetic patients, the American Diabetes Association (ADA) and the American Heart Association (AHA) have recommended the performance of lipid studies and glycosylated haemoglobin testing during routine monitoring of CKD patients[13,14,15].

Detailed studies have shown high levels of biomarkers for myocardial ischaemia among CKD patients[11,12]. Much of this increase has been attributed to reduced renal clearance, structural alterations of the cardiac muscle during uraemia, myocardial cell injury due to overproduction and release of pro-inflammatory cytokines, particularly tumour necrosis

factor-alpha, interleukin (IL)-1 and IL-6 and not myocardial ischaemia as such[16].

The main disadvantage in this study was the gross disparity in the number of patients belonging to each stage of CKD. As patients were selected not considering the stage of disease and they were staged afterwards, equal number could not be included in all the stages. There were no patients of stage I probably because our hospital is a tertiary care centre and only higher stages reach here.

Even though increase in mean level of troponin I with increasing stage of CKD and correlation with regard to CK-MB was documented in this study also, the high difference in the number of patients belonging to each group must be the reason for the difference not being statistically significant. Statistically significant difference can be documented only by doing a more detailed study including more patients belonging to each stage of the disease. A study that includes analysis of parameters for assessing other cardiac disorders along with myocardial ischaemia will be ideal for risk stratification.

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"Continuous effort – not strength or intelligence – is the key to unlocking our potential."

– WINSTON CHURCHILL.

ORIGINAL ARTICLE

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Vitamin D status in patients of congestive heart failure

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Abstract

Background: Vitamin D deficiency is a highly prevalent condition, present in approximately 50% of the general population. A growing body of evidence suggests that low vitamin D level adversely affect cardiovascular health including congestive heart failure.

Objectives: This study was performed to evaluate the vitamin D levels in patients of congestive heart failure (CHF), and find out its correlation with severity of heart failure.

Methods: 50 heart failure patients and 50 control subjects were recruited. Vitamin D levels (25-OH D) and parameters of calcium metabolism (serum calcium, serum phosphate, and serum alkaline phosphatase) were measured in fasting blood samples collected between January 2012 and December 2012.

Results: CHF patients had significantly reduced circulating levels of 25-hydroxy vitamin D ($p < 0.0001$), increased serum phosphorus levels ($p = 0.006$), and reduced serum calcium levels ($p = 0.001$) compared with the controls. Patients with ischaemic heart failure had lower vitamin D levels as compared to non-ischaemic ($p = 0.003$). Moreover, significant negative correlation was found between vitamin D level and severity of heart failure ($r = -0.812$; $p = < 0.0001$).

Conclusions: Serum vitamin D levels are significantly lower in congestive heart failure patients. Vitamin D level is found to be negatively correlated with severity of heart failure.

Keywords: Congestive heart failure, vitamin D, vitamin D deficiency.

Introduction

Cardiovascular disease is one of most common international health problem, and knowledge of factors linked to the disease is of utmost importance. Congestive heart failure is one of the leading causes of mortality and morbidity worldwide. Patients who develop heart failure are often hospitalised and have low quality of life score mainly due to worsening of HF[1]. Vitamin D has been traditionally associated primarily with bone health, and vitamin D deficiency leads to rickets in children and osteomalacia in adults is well known[2]. However, it is now known that adequate vitamin D status is important for optimal function of many organs and tissues throughout the body, including the cardiovascular system[3].

Vitamin D from the skin and diet is metabolised in the liver to 25-hydroxy vitamin D, which is used to determine a patient's vitamin D status; 25-hydroxy vitamin D is metabolised in the kidneys by the enzyme 25-hydroxy vitamin D-1α-hydroxylase (CYP27B1) to its active form, 1,25-dihydroxy vitamin D[4-7]. Although vitamin D has been classified as a vitamin for decades, clearly the 1, 25 (OH) 2D functions as a hormone, since it is produced predominantly by one organ (the kidney, although both vascular smooth muscle and endothelial cells may also be able to convert 25 (OH) D to1, 25 (OH) 2D) and exerts wide-range effects on numerous organs, including the cardiovascular system[3]. As vitamin D deficiency can be easily determined by blood testing and can be treated by supplementation, it is crucial to solidify knowledge of its prevalence and contribution to cardiovascular disease states and outcomes.

Material and methods

Fifty patients with congestive heart failure fulfilling inclusion and exclusion criteria were recruited in this study from January 2012 till December 2012. Fifty healthy controls who were free of any medical disease and were matched for age and gender were included in the study for comparison. Inclusion criteria were age > 18 years, congestive heart failure patients. These patients were diagnosed on the basis of symptoms typical of heart failure (ESC 2008 definition) (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling), signs typical of heart failure (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly) and objective evidence of a structural or functional abnormality of the heart at rest (ejection fraction, i.e., EF < 40%). They were further divided into 2 groups ischaemic and non-ischaemic (on the basis of ECG

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suggesting features of myocardial infarction and angiography suggestive of coronary artery disease) and were also graded according to NYHA Functional Classification. Exclusion criteria were age < 18 years, any non-cardiac chronic disease (such as chronic liver disease, chronic kidney disease, stroke or convulsion disorder, chronic lung disease, malabsorptive disorder, hypoparathyroidism), history of malignancy, isolated diastolic heart failure, valvular heart disease, severe anaemia, thyrotoxicosis, pregnancy, beriberi, intake of vitamin D supplements and therapy with anticonvulsants, glucocorticoids, rifampicin, isoniazid, anti-HIV drugs, ketoconazole. Laboratory investigations were performed within 24 hours of admission. Apart from routine investigation, serum vitamin D (25-OH D), serum calcium, serum phosphate, serum alkaline phosphatase, electrocardiogram, 2-D echocardiography, coronary angiography were performed. Vitamin D levels were interpreted as sufficient, insufficient, deficiency, and severe deficiency (Table I).

Table I: Interpretation of vitamin D level[12].

Serum 25-hydroxy vitamin D (ng/ml)	Vitamin D status
≤ 10	Severe deficiency
10 - 20	Deficiency
21 - 29	Insufficiency
≥ 30	Sufficiency (normal)

Collection of sample: Under strict aseptic precautions without using tourniquet, venous blood sample was collected from both cases and controls. Morning fasting blood sample was obtained and was immediately sent to the laboratory for evaluation. 2 ml blood was allowed to clot and then centrifuged to separate serum. The separated serum was stored in deep freezer at temperature < - 20% C in the biochemistry department. This serum was used to estimate the level of 25-hydroxy vitamin D using ELISA method (kit from DLD Diagnostika, Germany).

Two-dimensional echocardiography was performed with Sonos-4500 (Philips, Puducherry, India) with a 3.3 - mHz multiphase array probe in subjects lying in the left decubitus position. All echocardiographies were performed according to the recommendations of the American Society of Echocardiography and were analysed by a single experienced cardiologist who was blinded to all clinical details. Coronary angiography was interpreted as abnormal if ≥ 50% blockage on left main coronary artery or ≥ 70% blockage on any other coronary artery was found during angiography.

Statistical analysis

The results obtained were subjected to standard statistical methods for analysis and relevant conclusions were drawn from them. Results were expressed as mean (± standard deviation). Chi-square test, Mann-Whitney U test, Student's t-test, ANOVA test, Pearson's correlation test were used whenever applicable. $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics and biochemical parameters of two groups are shown in Table II and Table III respectively. The age of the patients ranged from 35 - 75 years with majority in 45 - 60 years age group. Vitamin D levels were below normal range in majority (92%) of congestive heart failure patients. The comparison of vitamin D levels in both the study groups are shown in (Table IV). Serum levels of 25-hydroxy vitamin D, phosphorus and calcium showed significant difference between the two groups ($p < 0.05$). Patients with ischaemic heart failure had lower vitamin D levels as compared to non-ischaemic patients ($p = 0.003$) (Table V). Moreover, significant negative correlation was found between vitamin D level and severity of heart failure ($r = -0.812$; $p = < 0.0001$) (Table VI).

Table II: Baseline characteristics of the two groups.

Parameters	Cases	Controls
Number	50	50
Age (years)	53 ± 10.41	49.68 ± 9.88
Sex (M: F)	32:18	33:17
BMI (kg/m^2)	25.5±2.7	24±2.4
Obesity	7	2
Diabetes	17	0
Hypertension	16	0
Smoker	12	6
Alcohol	10	4

BMI = body mass index.

Table III: Biochemical characteristics of the study population.

Parameters	Cases (N = 50)	Controls (N = 50)	p value*
Hb (g/dl)	11.9 ± 1.49	11.4 ± 1.38	> 0.05
Urea (mg/dl)	40.32 ± 12.06	30.02 ± 6.4	< 0.0001
Creatinine (mg/dl)	1.09 ± 0.33	0.96 ± 0.18	0.02
Calcium (mg/dl)	8.3 ± 1.09	9.1 ± 1.2	0.001
Phosphate (mg/dl)	4.1 ± 0.92	3.6 ± 0.75	0.006
ALP (IU/L)	67.9 ± 32.4	68.4 ± 32.4	> 0.05
Vitamin D (ng/ml)	16.98 ± 8.04	28.08 ± 11.38	< 0.0001

*Hb = haemoglobin; ALP = alkaline phosphatase; * p < 0.05 was statistically significant.*

Table IV: Comparison of vitamin D levels between the study groups.

Vitamin D level	No. of cases	No. of controls
Severe deficiency	11	0
Deficiency	23	14
Insufficiency	12	12
Normal	4	24
Total	50	50

Table V: Comparison of vitamin D levels in ischaemic and non-ischaemic heart failure patients.

Parameters	No.of patients	Angiography (normal)	Angiography (abnormal)	Vitamin D level (ng/ml)	p value
Ischaemic	35 (70%)	2	33	14.85 ± 7.39	0.003
Non-ischaemic	15 (30%)	15	0	21.95 ± 7.49	

Table VI: Comparison of NYHA (New York Heart Association) class and levels of vitamin D.

NYHA class	No. of cases	Vitamin D level (ng/ml)	p value
I	5	26.24 ± 8.94	< 0.0001
II	16	23.75 ± 4.37	
III	11	14.86 ± 4.7	
IV	18	9.69 ± 3.2	

Discussion

Congestive heart failure is one of the leading causes of mortality and morbidity. Although traditional risk factors such as diabetes, hypertension, and obesity are more prevalent in the population, there has been an increasing emphasis on nontraditional risk factors which can subsequently improve patient outcomes. In this study we found that serum 25-hydroxy vitamin D levels were reduced in CHF patients and the result was statistically significant ($p < 0.0001$). The associated increase of serum phosphorus as well as the reduced serum calcium levels of the CHF patients can be seen as a consequence of the low vitamin D status. The increase in blood urea and serum creatinine may be explained on the basis of congestive heart failure. Several observational studies have shown that vitamin D deficiency is a common finding in patients with cardiovascular disease and may increase the risk of developing HF. Pilz *et al* and Kim *et al* showed that significantly lower levels of 25 (OH) D and 1, 25 (OH) 2D were found in chronic HF patients[8,9]. Prospective studies conducted by Liu *et al* showed that poor vitamin D status is highly prevalent among heart failure patients and indicates an increased risk of mortality[10].

We also found that patients with ischaemic heart failure had lower vitamin D level as compared to non-ischaemic group resulting in significant difference between the two groups ($p < 0.05$). The inverse association of 25(OH) D levels and risk of myocardial infarction was previously confirmed by Giovannucci *et al* in a larger nested-case control study, an association that remained after controlling for known CVD risk factor[11]. In our study, we found that patients with higher NYHA class were having lower vitamin D levels. This inverse relation can be explained on the basis of reduced outdoor activities, decreased intake, and can be attributed to the disease itself. The limitations of our study involved a small sample size and cross-sectional nature of the study.

Conclusion

We therefore conclude that serum vitamin D levels are lower in the majority of congestive heart failure patients and were associated with severity of disease. Further work is needed to assess whether vitamin D has a causative role in congestive heart failure and whether vitamin D replacement therapy will be beneficial in these cases.

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A study of CSF C-reactive protein levels in patients of meningitis

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Abstract

Introduction: The aetiologic diagnosis of meningitis remains a problem in clinical practice as CSF biochemical analysis and cellular response often overlap. Thus there is a need of rapid and aetiological diagnosis of meningitis for better clinical outcome. Tests like PCR and ELISA are helpful but costly, not easily available, and not easily performed. In such circumstances the determination of CSF CRP appears to provide a new dimension to the specific diagnosis of meningitis.

Material and methods: The present study was carried out on 70 patients of meningitis admitted to the Medicine and Neurology wards of JA Group of Hospitals, Gwalior from July 2006 to October 2007. The quantitative estimation of CSF CRP level was done using a latex turbidimetric method.

Observations: In the present study, 30 cases of pyogenic meningitis, 36 cases of tubercular meningitis, and 4 cases of viral meningitis were included making a total of 70 cases. At CSF C-reactive level of 10 mg/l, the test characteristics were highly favourable with 90% sensitivity and 97% specificity for pyococcal meningitis as compared to tubercular and viral meningitis ($p < 0.0001$). In tubercular meningitis 91.6%, and all viral meningitis patients have CSF C-reactive level < 5 mg/l.

Conclusion: CSF C-reactive level can be used to differentiate pyogenic from non-pyogenic meningitis consistently, and with high level of sensitivity, and specificity. A low level below 5 mg/l can be used to rule-out a diagnosis of pyogenic meningitis.

Key words: Meningitis, pyococcal meningitis, tubercular meningitis, C-reactive protein, viral meningitis.

Abbreviations: CSF CRP = Cerebrospinal fluid C-reactive protein, TBM = Tubercular meningitis.

Introduction

Meningitis is defined as infection involving the subarachnoid space and is associated with CNS inflammatory reaction. The therapeutic outcome in meningitis is directly proportional to the time of starting the specific therapy. The dictum is: "treatment delayed is treatment denied".

Meningitis can be of pyogenic, tubercular, viral, fungal, spirochetaetal or of parasitic origin.

The aetiologic diagnosis of meningitis remains a problem in clinical practice as CSF biochemical analysis and cellular response often overlap. Thus there is a need of rapid and aetiological diagnosis of meningitis for better clinical outcome. Tests like PCR and ELISA are helpful but costly, not easily available, and not easily performed. In such circumstances the determination of CSF CRP appears to provide a new dimension to the specific diagnosis of meningitis.

C-reactive protein is an acute phase reactant of "Pentraxin" group of family, discovered in 1930 by Tillet *et al*. It is synthesised exclusively in the liver and is secreted in large quantities within 6 hrs of an acute inflammatory stimulus in serum or fluids associated with the affected tissues. Raised CSF CRP level in meningitis is due to passive diffusion across the highly inflamed meninges. Hence increased serum CRP levels signify acute phase response, thus increased CSF CRP signifies meningeal involvement.

CSF CRP testing appears to be an attractive option for the rapid diagnosis of pyogenic meningitis and hence many studies have been done to evaluate this role of CSF CRP. But there is some conflicting data regarding the use of this test and it has yet to become a standard part of the meningitis diagnostic battery. Many of the previous studies in relation to CSF CRP and meningitis have used a qualitative CRP assay. There is also a paucity of data in the adult population as these studies were done predominantly in the paediatric population. Keeping this in mind, the present study has been undertaken and best possible efforts have been made to do away with the drawbacks of previous studies in this subject.

Thus the present study has been designed to evaluate the diagnostic utility of CSF CRP levels in clinically diagnosed cases of meningitis.

Material and methods

The present study was carried out on 70 patients of meningitis admitted to the Medicine and Neurology wards

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of JA Group of Hospitals, Gwalior from July 2006 to October 2007.

The patients (> 12 yrs of age) admitted with suspicion of meningitis who later prove to be having tubercular, pyogenic, or viral meningitis were included in this study group after taking appropriate consent, and approval from the ethical committee of the medical college.

Attempts were made to make a provisional diagnosis of the type of meningitis on the basis of characteristic features in history and physical examination. The final diagnosis was based on the clinical criteria and biochemical, cytological and bacteriological examination of CSF. A turbid CSF with decreased or absent glucose and high protein content along with increased PMN leucocytes was taken as indicative of pyogenic meningitis. A clear CSF with or without cobweb, some reduction of glucose, moderately increased protein along with increased lymphocytes, negative Gram's stain, and sterile on routine culture was taken as tubercular meningitis. A clear CSF, normal glucose, mild increased protein along with increased Lymphocytes, negative Gram's stain, and sterile on routine culture was taken as viral meningitis.

The quantitative estimation of CSF CRP level was done using a latex turbidimetric method.

Latex particles coated with specific anti-human CRP are agglutinated when mixed with sample containing CRP. The agglutination causes an absorbance change, dependent upon the CRP content of the patient's sample that can be quantified by comparison from a calibrator of known CRP concentration.

Observations

70 cases were studied according to age and sex in the study. 34 cases belonged to 20 to 40 years age group, comprising 48.6% followed by 17 cases belonging to < 20 years age group, comprising 24.3%. In the age group of 41 to 60 years and > 60 years the number of cases were 14 and 5 respectively. It is evident from the Table I that 48 cases were male, making up about 68.5% of the total cases with 22 females (31.5%).

As per the CSF findings, 30 patients were of pyogenic, 36 were of tubercular meningitis, and 4 were of viral meningitis in our study. Fever was the most common presenting complaint (Table II) in the cases of pyogenic and tubercular meningitis, whereas in viral meningitis headache was the most common complaint. Headache and vomiting as presenting complaint were more common in tubercular meningitis than pyogenic meningitis. About 70% of the patients of pyogenic meningitis presented with some alteration of consciousness as compared to less than 50% in tubercular meningitis. Convulsions were a more common complaint in viral (50%) as compared to pyogenic (10%), and tubercular (2.77%) meningitis.

Table III depicts the biochemical and cytological features of CSF examination. 63% of cases of pyogenic meningitis had a CSF cell count of more than 400/cu mm as compared to 11% of tubercular meningitis, and 0% of viral meningitis. All the cases of viral and 66% cases of tubercular meningitis had cell count of less than 200/cu mm. 50% of cases of pyogenic meningitis had a CSF protein level of > 200 mg/dl, whereas this high level of protein was present only in 16.7% of cases of tubercular and none of the cases of viral meningitis. All the cases of viral group had a protein level of < 100 mg/dl, and about 70% of cases of tubercular meningitis had a protein level of < 150 mg/dl. 90% of cases of pyogenic meningitis had a CSF to blood glucose ratio of less than 0.4, about 70% of tubercular meningitis cases had the ratio below this level, while in the viral meningitis group 75% cases had this ratio above 0.5.

The mean CSF CRP levels were almost similar in the age group > 20 years, 20 to 40 years, and 41 to 60 years but it seems to be almost double in > 60 years age group. However, it was statistically insignificant (Table IV). In our study males and females had similar levels of CSF CRP.

As shown in Table V, in the TB meningitis group most of the cases 33 (91.6%) were having a CSF CRP level in the lower range of < 5 mg/l, and one case in the range of 10 to 15 mg/l. Similarly, in the viral meningitis group all the cases are having a CSF CRP in the range < 5 mg/l. In comparison to these two, the pyogenic meningitis group is having 26 cases (86.6%) with a CSF CRP levels above 10 mg/l. Thus, it is very clear from the above table that while in the non-pyogenic group majority of cases are concentrated in the low CSF CRP zone it is just the reverse in the pyogenic meningitis group.

As shown in Table VI, pyogenic meningitis group has a mean level of 16.223 mg/l, which is much higher as compared to the mean levels in other two groups (2.244 mg/l in TB meningitis group and 0.875 mg/l in viral meningitis group). The calculated p values show that the difference is statistically very highly significant ($p < 0.0001$) when the means of pyogenic group is compared with the other two. However, the difference between the means of viral meningitis and TB meningitis group was found to be statistically insignificant ($p > 0.19$).

As seen in the Table VII, 30% (9 cases) of the pyogenic meningitis cases were culture positive, and the remaining 70% (21 cases) were culture negative. The culture positive group had more cases (55.5%) with CSF CRP levels more than 20 mg/l as compared to only 2 cases (13%) in culture negative group.

Table I: Age and sex distribution of cases in relation to type of meningitis.

S. No.	Type of meningitis	< 20 years				20 - 40 years				41 - 60 years				> 60 years				Total		
		F	M	Total	%	F	M	Total	%	F	M	Total	%	F	M	Total	%	F	M	Total
1.	Pyogenic	1	5	6	8.57	5	8	13	18.57	0	6	6	8.57	2	3	5	7.14	8	22	30
2.	TB	2	7	9	12.86	8	12	20	28.57	3	4	7	10.02	0	0	0	0	13	23	36
3.	Viral	1	1	2	2.85	0	1	1	1.43	0	1	1	1.43	0	0	0	0	1	3	4
Total		4	13	17	24.28	13	21	34	48.57	3	11	14	20	2	3	5	7.14	22	48	70

Table II: Frequency of presenting complaints in different disease groups.

S. No.	Presenting complaints	Pyogenic meningitis (n = 30)		Tubercular meningitis (n = 36)		Viral meningitis (n = 4)	
		No. of cases	%	No. of cases	%	No. of cases	%
1.	Fever	29	96.66	31	86.11	3	75
2.	Headache	23	76.66	30	83.33	4	100
3.	Vomiting	17	56.66	28	77.77	2	50
4.	Convulsions	3	10	1	2.77	2	50
5.	Altered Sensorium	21	70	17	47.22	2	50

Table III: CSF examination features (cytological and biochemical) in different types of meningitis.

S. No.	Features	Pyogenic meningitis (n = 30)		Tubercular meningitis (n = 36)		Viral meningitis (n = 4)	
		No. of cases	%	No. of cases	%	No. of cases	%
1.	CSF cell counts (cu mm)	–	–	–	–	–	–
	≤ 100	00	0	12	33.3	2	50
	101 – 200	01	3.3	12	33.3	2	50
	201 – 300	04	13.3	07	19.4	0	0
	301 – 400	06	20	01	2.8	0	0
	> 400	19	63.3	04	11.1	0	0
2	CSF protein levels (mg/dl)	–	–	–	–	–	–
	< 100	00	0	14	38.9	4	100
	101 – 150	05	16.7	11	30.5	0	0
	151 – 200	10	33.3	05	13.9	0	0
	> 200	15	50	06	16.7	0	0
3	CSF to blood glucose ratio	–	–	–	–	–	–
	< 0.3	16	53.3	10	27.8	01	25
	0.31 – 0.4	11	36.7	15	41.7	00	0
	0.41 – 0.5	03	10	08	22.2	00	0
	> 0.5	00	0	03	8.3	03	75

Table VIII describes the various test characteristics of CSF CRP levels for different cut-off values. The maximum sensitivity of the test that can be achieved is for a cut-off value of 5 mg/l (93.33%). At this level of sensitivity, the other test characteristics are also acceptable, thus making it a good screening test at this cut-off level.The maximum specificity of the test is at the level of 15 mg/l but this is at the expense of low sensitivity (66.66%). At the CSF CRP

level of 10 mg/l the test characteristics are highly favourable with 90% sensitivity and 97.5% specificity. Thus it is clear that the ideal cut-off value that should be used for diagnosing pyogenic meningitis by CSF CRP level should lie between 5 - 10 mg/l.

Table IV: Distribution of cases with age and CSF CRP levels.

S. No.	Range of CSF CRP (mg/l)	No. of cases in different age groups				Total
		a ≤ 20 yrs	b 21 - 40 yrs	c 41- 60 yrs	d > 60 yrs	
1.	0 - 5.0	9	23	7	0	39
2.	5.1 - 10.0	1	0	2	1	4
3.	10.1 - 15.0	4	2	1	1	8
4.	15.1 - 20.0	2	4	3	3	12
5.	> 20.0	1	5	1	0	7
Total	→	17	34	14	5	70
Mean CRP levels (mg/l)		7.788	7.556	7.886	14.26	–

Table V: Case distribution on the basis of type of meningitis and CSF CRP level.

S. No.	Range of CSF CRP (mg/l)	No. of cases in different type of meningitis groups			Total
		a TB	b Pyogenic	c Viral	
1.	0 - 5.0	33	2	4	39
2.	5.1 - 10.0	2	2	0	4
3.	10.1 - 15.0	1	7	0	8
4.	15.1 - 20.0	0	12	0	12
5.	> 20.0	0	7	0	7
Total	→	36	30	4	70
Mean CRP levels (mg/l)		2.244	16.223	0.875	–

Table VI: Mean CSF CRP levels in different types of meningitis.

S. No.	Type of meningitis	No. of cases	Mean CRP levels (mg/l)	Standard deviation
1.	Tubercular	36	2.244	2.06
2.	Pyogenic	30	16.223	5.813
3.	Viral	4	0.875	0.403
Total		70	–	–

TB meningitis group: Mean = 2.244, SD = ± 2.060

Pyogenic meningitis group: Mean = 16.223, SD = ± 5.813

Viral meningitis group: Mean = 0.875, SD = ± 0.403

{ TB vs pyogenic: p value < 0.0001, statistically highly significant

Viral vs TB: p value > 0.19, statistically insignificant

Pyogenic vs viral: p value < 0.0001, statistically highly significant}.

Table VII: Relation of CSF CRP with CSF bacteriological culture in pyogenic meningitis.

S. No.	Range of CSF CRP (mg/l)	No. of cases with culture positive or negative pyogenic meningitis		Total
		Culture positive	Culture negative	
1.	0 - 5.0	0	2	2
2.	5.1 - 10.0	0	2	2
3.	10.1 - 15.0	0	7	7
4.	15.1 - 20.0	4	8	12
5.	> 20.0	5	2	7
Total	→	9	21	30
Mean CRP levels (mg/l)		21.767	13.848	–

Group a: Culture positive group

n = 9 , Mean = 21.767 , SD = ± 4.243

Group b: Culture negative group

n = 21 , Mean = 13.484 , SD = ± 4.695

{Statistical difference of two means in above two groups (a and b) p < 0.0002, statistically highly significant}.

Discussion

In clinical practice, it still remains a problem to differentiate between pyogenic and tubercular meningitis, as CSF biochemical and cellular responses often overlap. This becomes more difficult in populations where tubercular meningitis is prevalent as *Mycobacterium tuberculosis* is not always easily and reliably identifiable by established techniques. Because of long-term therapeutic and prognostic implications of tubercular meningitis, additional diagnostic parameters would be of great importance. CRP is fast gaining the acceptance for distinction of pyogenic from non-pyogenic infections of central nervous system.

The present study was conducted in the department of Medicine, GR Medical College, Gwalior, during a period of 16 months from July 2006 to October 2007. The diagnosis of meningitis was based on existing history and clinical examination supported by laboratory investigations and findings of CSF analysis.

In the present study, 30 cases of pyogenic meningitis, 36 cases of tubercular meningitis, and 4 cases of viral meningitis were included making a total of 70 cases.

Out of the total 70 cases of meningitis, 34 cases belonged to 20 to 40 years age group comprising 48.6%, followed by 17 cases belonging to < 20 years age group, comprising 24.3%. In the age group of 41 to 60 years and > 60 years, the number of cases were 14 (20%) and 5 (7.1%) correspondingly. In the pyogenic and tubercular

Table VIII: Sensitivity and specificity for different CSF CRP levels as a diagnostic test for pyogenic meningitis.

S. No.	Level of CSF CRP used as a cut-off for diagnosing Pyogenic meningitis (mg/l)	TP	TN	FP	FN	Sensitivity $\frac{TP}{TP+FN}$ %	Specificity $\frac{TN}{TN+FP}$ %	Positive predictive value $\frac{TP}{TP+FP}$ %	Negative predictive value $\frac{TN}{TN+FN}$ %
1.	5.0	28	37	3	2	93.33	92.50	90.32	94.87
2.	10.0	27	39	1	3	90.00	97.50	96.42	92.85
3.	15.0	20	40	0	10	66.66	100	100	80.00

meningitis group, maximum number of cases (43.3% and 56 % respectively) were in the 20 to 40 years age group, but in viral meningitis group, maximum number of cases (50%) were in the age group of < 20 years. So in the present study almost half of the cases were in the 20 to 40 years age group and one-fourth of the cases in < 20 years age group. This pattern of case distribution was similar in both tubercular and pyogenic meningitis group but differed in viral meningitis group, with half of the cases of viral meningitis in the < 20 years age group. These findings are consistent with other studies[8,15].

In the present study, 48 cases were males and 22 cases were females, making up 68.5% and 31.5% of the cases respectively. Thus, there was a male preponderance in our study with a male to female ratio of more than 2:1. The previous studies have reported a highly variable sex incidence of meningitis[4,5].

In the TB meningitis group, most of the cases (91.6%) had a CSF CRP level in the range of < 5 mg/l, and one case in the range of 10 to 15 mg/l. Similarly, in the viral meningitis group, all the cases had a CSF CRP in the range <5 mg/l. In comparison to these two the pyogenic meningitis group had 26 cases (86.6%) with a CSF CRP level above 10 mg/l. 19 cases had a CSF CRP level of >15 mg/l, and all these cases were in the pyogenic meningitis group.

The mean CSF CRP levels in these three groups was calculated and compared. The pyogenic meningitis group had a mean level of 16.223 mg/l, which is much higher as compared to the mean levels in other two groups (2.244 mg/l in TB meningitis group and 0.875 mg/l in viral meningitis group). The calculated p values showed that the difference is statistically very highly significant ($p < 0.0001$) when the means of pyogenic group is compared with the other two similar to other studies[6,9,11,14]. However, the difference between the means of viral and TB group was found to be statistically insignificant ($p > 0.19$).

In the present study, cases of pyogenic meningitis were further subdivided into culture positive and culture negative group, and there distribution in relation to CSF CRP level was studied. It was seen that 30% (9 cases) of the pyogenic meningitis cases were culture positive and the remaining 70% (21 cases) were culture negative. The culture positive group had more cases (55.5%) with CSF CRP levels more than 20 mg/l as compared to only 2 cases (13%) in culture negative group.

The mean CSF CRP levels in the culture positive (21.767 mg/l) group was higher as compared to culture negative (13.848 mg/l) group. This difference in two means was found to be statistically highly significant ($p < 0.0002$). Thus our study suggests that those with culture positive pyogenic meningitis have a higher CRP levels as compared to those who are culture negative. The culture positive rate in our study was 30%, which is low as compared to that reported in previous studies[9,11,13,14] in which the culture positive rates were around 70 to 85 % in all the studies. However, the finding of significantly higher levels of CSF CRP levels in the culture positive group is consistent with that found in these studies.

The poor prognostic factors taken were age >50 years, diabetes mellitus, glasgow coma score <8, focal neurologic deficit, seizures and alcoholism. These risk factors were used after reviewing previous studies and standard text available on the matter (Adams and Victor's, 2005; Bohr *et al* 1983; Dodge *et al*, 1965; Durand *et al*,1993; Feldman, 1977; and Fraser *et al* 1973). There were 16 cases who had at least one of these poor prognostic factors and the remaining 14 cases had none of the poor risk factors. The case distribution was almost similar in both the groups with respect to the CSF CRP levels. The means of two groups were compared and the difference was statistically insignificant ($p > 0.3$). Thus in our study CSF CRP level did not bear any correlation with the poor prognostic factors for pyogenic meningitis.

In our study, assessment of CSF CRP level as a diagnostic test for pyogenic meningitis was by calculating various test characteristics of CSF CRP levels for different cut-off values. The maximum sensitivity of the test was achieved for a cut-off value of 5 mg/l (93.33%). At this level of sensitivity, the other test characteristics were also acceptable making it a good screening test at this cut-off level. The maximum specificity of the test was at the level of 15 mg/l but this is

at the expense of low sensitivity (66.66%). At the CSF CRP level of 10 mg/l, the test characteristics were highly favourable with 90 % sensitivity and 97.5% specificity. Thus it is clear from our study that CSF CRP level is highly sensitive and specific for pyogenic meningitis, and the cut-off value that should be used for diagnosing pyogenic meningitis by CSF CRP level should lie between 5 - 10 mg/l. In the study of Gerdes *et al* (1998) a meta-analysis of literature published on CSF CRP levels from 1980 onwards was done and both the sensitivity and specificity of the CSF CRP test were found to be 94 %. The sensitivity and specificity in other previous studies were found to be as follows: Corall *et al* (1981)[3] 100% and 94 %, Benjamin *et al* (1984)[1] 66% and 96%, Eiden *et al* (1986)[7] 82% and 96%, John *et al* (1990)[10] 91% and 99%, Park *et al* (2003)[11] 100% and 88%.

Summary and conclusion

CSF C-reactive protein level is one of the best parameter to diagnose pyogenic meningitis.

CSF C-reactive protein level can be used to differentiate pyogenic meningitis from non pyogenic meningitis consistently and with high level of sensitivity and specificity. A CSF C-reactive protein level of more than 15 mg/l by latex turbidimetric method can be used to confirm the diagnosis of pyogenic meningitis and rule-out tubercular or viral meningitis. A level below 5 mg/l can be used to rule-out a diagnosis of pyogenic meningitis.

CSF C-reactive protein levels did not correlate with the poor prognostic factors for pyogenic meningitis. So it cannot be used as a prognostic indicator in cases of pyogenic meningitis.

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"Happiness is not an achievement; it is a choice.
Nothing can make you happy until you make the decision to be happy ...
And there's no need to be perfect to inspire others;
let people get inspired by how you deal with your imperfections. "

– Brahma Kumaris.

ORIGINAL ARTICLE

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Almotriptan versus ibuprofen in migraine: A randomised placebo-controlled trial

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Abstract

Objective: The objective of this study was to compare the efficacy of almotriptan and ibuprofen in migraine.

Material and methods: This study was a randomised placebo-controlled trial conducted in a tertiary care teaching hospital located in a rural area. Migraine patients with < 8 attacks/month were included.

Results: A total of two hundred and sixteen migraine patients were randomised to almotriptan 12.5 mg (73), ibuprofen 400 mg (71) and placebo (72). The efficacy was assessed by headache relief, and headache freedom at 2 hours and 24 hours. Two-hour headache relief was noted in 73.97% in almotriptan, 53.52% in ibuprofen and 13.88 % in placebo groups. Headache freedom was achieved in 23 (31.5) % in almotriptan, 20 (28.16)% in ibuprofen, and 2 (2.7%) in placebo groups. Almotriptan was superior to ibuprofen and placebo in relieving headache at 2 hours and at 24 hours. Side-effects were noted in 9 patients in almotriptan, 8 in ibuprofen, and 3 in placebo, all of which were nonsignificant.

Conclusion: We concluded that almotriptan is superior to ibuprofen in relieving headache, associated symptoms, and functional disability.

Keywords: Migraine, almotriptan, ibuprofen, acute attack, randomised controlled trial treatment.

Introduction

Migraine is a chronic, recurrent, disabling, neurovascular disorder. For treating acute migraine attacks, a number of drugs are used, including ergot alkaloids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen and triptans. Both Cox I and Cox II inhibitors have been investigated and found to be effective in migraine[1,2]; however, rofecoxib has been withdrawn due to toxicity[3]. The reported efficacy of NSAIDs is 42 - 72%[1,4-7]. NSAIDs are in use because of their predictable response, low cost, and well known side-effect profile. Triptans are a new class of drugs, which are 5-HT1B-D agonists, quick acting and have low gastrointestinal toxicity. Rizatriptan was superior to ibuprofen in relieving headache, associated symptoms, and functional disability in the placebo-controlled trial[8]. Almotriptan has been shown to be effective and tolerable, and thus represent a first-line treatment for acute migraine attacks. The clinical efficacy and tolerability of almotriptan has been tested in two controlled, double-blind randomised clinical trials against placebo[9,10,11]. In a study especially looking at sumatriptan non responders, subjects recieving almotriptan 12.5 mg, compaired with placebo were more likely to be headache free at 2 hours[12]. The decision to choose a new drug in based not only on its efficacy compared to placebo but also its relative advantage over other available drugs. There is no study comparing almotriptan with other NSAIDs. We therefore report the results of a randomised placebo-controlled trial (RCT) comparing almotriptan with ibuprofen and placebo.

Material and methods

The present study was conducted in a tertiary care teaching hospital situated in a rural area during 2012 - 2014 and was duly approved by the local ethics committee. The patients were recruited from out-patient service of the Neurology Department. Migraine patients above the age of 14 years were diagnosed on the basis of international Headache Society criteria[13]. Patients with mild (grade-I) headache, headache with recurrent vomiting, or more than 8 attacks per month, pregnant or lactating mothers, and those on oral contraceptives, or with a history of drug allergy, intractable hypertension, renal or hepatic failure, coronary artery disease, pulmonary, psychiatric or other neurological diseases were excluded. The patients were subjected to a detailed medical history and physical examination as per fixed protocol. The patients were randomised into almotriptan, ibuprofen, and placebo using computer-generated random numbers. Randomisation was done by one investigator and evaluation by another. The patients were asked to record severity of headache, functional disability, and associated symptoms such as nausea, vomiting, phonophobia, photophobia and allodynia before and 2 hours after medication, in a headache diary. Relapse

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of headache within 24 hours was also noted. Headache relapse was defined as occurrence of moderate-to-severe headache within 24 hours of dosing in patients who initially had relief of pain 2 h after medication. The severity of headache was graded on a 0 - III scale (0 = normal, grade I = mild, grade II = moderate and grade III = severe). Functional disability was graded as 0 = normal, I = daily activity mildly impaired, II = daily activity moderately impaired, III = daily activity severely impaired, and IV = inability to perform daily activity requiring bed rest[8]. The severity of associated symptoms of nausea, vomiting, photophobia, and phonophobia were also graded on a 0 - III scale: O = normal, I = mild, II = moderate, III = severe. The patients were advised to take study medication almotriptan 12.5 mg, ibuprofen 400 mg or placebo if the headache was moderate-to-severe. Medication was provided in identical packets. Rescue medication piroxicam 20 mg was advised if moderate-to-severe headache persisted 2 hours after initial medication.

The patients were subjected to blood counts, urinalysis, blood sugar, serum creatinine, bilirubin, serum transaminases, and electrocardiogram. Any side-effect up to 24 hours after medication was recorded.

Efficacy measurement

Efficacy of drug was evaluated at the 1-month follow-up visit or after 2 or more attacks, which were documented in the headache diary. The primary end-point was percentage of patients having pain relief at 2 hours. Pain relief was considered if severity of headache was reduced to grade I or 0. The secondary end-point was percentage of patients with relief of associated symptoms, functional disability at 2 hours and pain freedom at 24 hours.

Sample size calculation and statistics

The calculated sample size was 216, taking alpha = 0.05, critical difference between the drugs 15% and standard deviation (SD)[2]. The power of test as evaluated for Mann – Whitney U-test was 78.62%. The baseline characteristics between groups were compared by independent t, χ^2 and Fisher's exact tests. The efficacy of drugs between the groups was analysed by Mann-Whitney U-test and within the same group by Wilcoxon signed ranked test. The numbers of patients with headache relief at 2 hours and relapse within 24 hours were compared by χ^2 test.

Results

In this study, 236 migraine patients fulfilled the inclusion criteria during the study period. Ten patients were excluded due to lack of consent. Seventy six patients were randomised to almotriptan, 74 to ibuprofen and 76 to placebo. Four patients in placebo and 3 each in ibuprofen and almotriptan were lost from follow-up (Fig. 1). Our results, therefore, are based on 216 migraine patients whose age ranged between 14 and 58 (mean 33.52) years, 142 of whom were females. 120 patients had migraine without aura. The duration of migraine ranged between 6 and 260 (mean 65.99) months. The mean frequency of migraine attacks was 4.28 (range 2 - 8) per month. One hundred and eleven patients had moderate and 105 severe headache. The mean headache score was 2.48 ± 0.50, associated symptoms score 2.06 ± 0.29 and functional disability score 2.42 ± 1.4. Seventy-three patients were randomised to almotriptan, 71 ibuprofen and 72 placebo groups. The demographic and clinical variables of these groups were not significantly different (Table I).

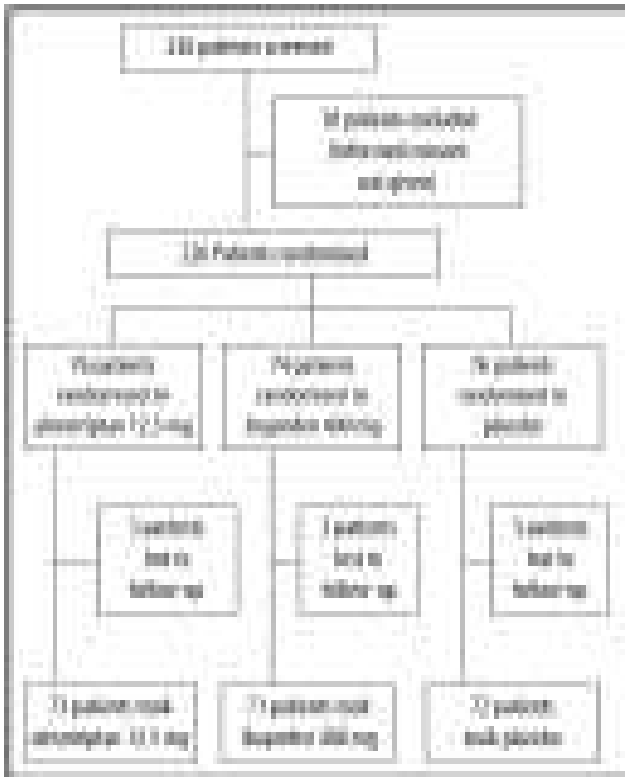

Fig. 1: *Flow chart showing randomisation of migraine patients.*

Efficacy

In the present study, two-hour headache relief was achieved by almotriptan in 54 (73.9%), by ibuprofen in 38 (53.52%) and placebo in 10 (13.88%) patients. Two-hour headache freedom was achieved by almotriptan in 23 (31.7%), by ibuprofen in 20 (28.16%) and by placebo in 2 (2.7%) patients. Almotriptan was significantly better than ibuprofen in relieving headache (p = 0.0001) but not in achieving pain freedom (p = 0.38). The headache score at 2 hours

compared to baseline was significantly greater in almotriptan (p = 0.0001) and ibuprofen (p = 0.0001). Functional disability and associated symptoms were also significantly reduced at 2 hours in both almotriptan and ibuprofen groups (Table II). Comparing the efficacy between the groups revealed significant improvement in headache score, associated symptoms, and functional disability both in almotriptan and ibuprofen compared to placebo. The difference between almotriptan and ibuprofen was significant (p = 0.006).

The patients in almotriptan resulted in significant improvement in headache score and significant relief in associated symptoms and functional disability compared to ibuprofen (Table III). Twenty four- hour headache relapse in the patients who responded at 2 hours was noted in 8 (14.81%) in almotriptan, 13 (34.21%) in ibuprofen, and 8 (80%) in placebo groups. This difference was not significant (p = 0.87). A significantly higher number of patients needed rescue medication (piroxicam 20 mg dispersible) in the placebo group (63) compared to the almotriptan (29) and ibuprofen (31 patients; p < 0.0001) groups. Requirement of rescue medication was also significantly higher in ibuprofen compared to almotriptan (p = 0.04).

Table I: The comparison of demographic and clinical variables of migraine patients between study and control groups.

Variables	Almotriptan (n = 73)	Ibuprofen (n = 71)	Control (n = 72)
Age (yrs)	33.41 ± 10.64	33.59 ± 11.38	33.57 ± 10.25
Female	46	47	49
Number of attacks	4.25 ± 1.4	4.18 ± 1.2	4.42 ± 1.38
Duration (months)	73.97 ± 53.42	70.32 ± 63.53	63.28 ± 52.21
Family history	38	39	37
Nausea	72	70	71
Vomiting	65	64	64
Photophobia	71	69	70\
Phonophobia	70	69	68
Functional disability-I			
I	4	8	7
II	38	37	34
III	30	25	30
IV	1	1	1
Severity of headache-			
Moderate	36	37	38
Severe	37	34	34
Duration of attack (hours)	14.95 ± 9.08	13.08 ± 7.8	14.65 ± 10.22

Table II: Efficacy of almotriptan, ibuprofen, and placebo in patients with migraine.

Drugs	Before treatment (mean ± SD)	2 hour after treatment (mean ± SD)	Z value	P
Almotriptan (73)				
Headache score	2.51±0.50	1.05±0.96	6.79	0.0001
Functional disability score	2.38±0.62	1.33±0.88	6.42	0.0001
Associated symptom score	2.12±0.33	0.85±0.84	6.75	0.0001
Ibuprofen (52)				
Headache score	2.48±0.50	1.38±1.11	5.75	0.0001
Functional disability score	2.27±0.66	0.90±0.91	6.71	0.0001
Associated symptom score	2.04±0.20	1.13±0.81	5.89	0.0001
Placebo (50)				
Headache score	2.47±0.50	2.50±0.52	0.876	0.48
Functional disability score	2.35±0.66	2.39±0.68	0.745	0.89
Associated symptom score	2.01±0.27	2.05±0.29	0.621	0.67

Table III: Comparison of efficacy of almotriptan, ibuprofen, and placebo in acute migraine attack (Z/p values).

Sysmptoms	Almotriptan vs ibuprofen	Almotriptan vs placebo	Ibuprofen vs placebo
Headache score	1.74/0.08	6.34/0.0001	3.93/0.0001
Associated symptoms	0.49/0.63	3.89/0.0001	2.59/0.010
Functional disability	1.32/0.19	3.68/0.0001	3.03/0.002

Twenty patients developed side-effects in our study: 9 in almotriptan (palpitations in 6, somnolence in 1, and gastric discomfort in 2), 8 in ibuprofen (gastric discomfort in 6 and palpitations in 2) and 3 in the placebo group (gastric discomfort in all). The side-effects were mild-to-moderate and could be easily controlled without any protocol violation.

Discussion

Our study reveals that almotriptan and ibuprofen were superior to placebo in relieving pain, associated symptoms and functional disability at 2 hours compared to placebo. These are in agreement with the earlier studies in which almotriptan 12.5 mg was superior to placebo[9,10]. Efficacy of almotriptan in relieving headache has been reported to be from 58.5% to 70.3% and 2-hours pain freedom 30% to 45.3%[9,10]. In our study, almotriptan resulted in headache relief in 73.9% and headache freedom in 31.5% patients. Ibuprofen resulted in headache relief in 53.52% and headache freedom in 28.16% patients. The efficacy of ibuprofen in earlier studies has been reported to be 42 - 70%[4,7,16,17].

In our study comparing almotriptan with ibuprofen, almotriptan was better in relieving pain, associated symptoms and functional disability at 2 hours. Almotriptan has been compared with other triptans and is reported to be similar to sumatriptan, frovatriptan in 2-hours pain relief and 24-hours headache freedom[14,15]. Acetaminophen, aspirin and NSAIDs in migraine have been found to be effective and well tolerated in adults and children[4,17]. In childhood migraine, ibuprofen has been found to be superior to acetaminophen[4]. There is however no study comparing the relative efficacy of almotriptan and NSAIDs. Triptans, especially sumatriptan, have been compared with naproxen, indomethacin, aspirin, and ibuprofen[18,19,20]. In an RCT, ibuprofen resulted in headache relief in 62.5%, sumatriptan in 55.8%, and headache freedom was 33.2% and 37.1% patients respectively, which were not significant[17]. In our study, almotriptan resulted in significant pain relief, reduction in associated symptoms and functional disability compared to ibuprofen. Gastrointestinal side effects were more common with ibuprofen and palpitations with almotriptan; however, the side-effects were not severe enough to warrant discontinuation in any patient.

Our study is limited by the relatively small number of patients. As the study was conducted in a single centre, there is homogeneity in patient selection and low inter-rater variability. Efforts were made to blind the randomising and evaluating investigators and medication was provided in identical packets, to eliminate bias.

Conclusions

Both almotriptan and ibuprofen are superior to placebo in aborting acute migraine attacks. Almotriptan 12.5 mg is superior to ibuprofen in relieving headache, associated symptoms, and functional disability.

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REVIEW ARTICLE

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Spontaneous bacterial empyema (SBEM)

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Abstract

Though spontaneous bacterial peritonitis is a well-known entity, spontaneous bacterial empyema (SBEM), also known as spontaneous bacterial pleuritis (SBPL) is a rare infective complication of a pre-existing hydrothorax in patients with portal hypertension. Spontaneous bacterial pleuritis or empyema, defined as spontaneous infection of the pleural fluid, represents a distinct complication of hepatic hydrothorax with a different pathogenesis, natural history, clinical features, diagnostic findings, and treatment strategy from those of empyema secondary to pneumonia. It is a frequent, though not so frequently diagnosed, complication of hepatic hydrothorax and portends a poor prognosis.

Key words: Spontaneous bacterial empyema (SBEM), Spontaneous bacterial pleuritis (SBPL), Spontaneous bacterial peritonitis (SBP), hepatic hydrothorax.

Introduction

Patients with end-stage liver disease (ESLD) often suffer from complications of portal hypertension. Hepatic hydrothorax is defined as a significant transudative pleural effusion, usually greater than 500 ml, in patients with portal hypertension without any other identifiable aetiology like an underlying pulmonary, pleural, or cardiac disease[1]. It is believed to be caused by fluid retention and passage of ascites from the peritoneal to the pleural cavity along a pressure gradient, through small diaphragmatic defects located in the tendinous portion of the diaphragm[1].

The presence of portal hypertension and not cirrhosis is the sine qua non for the development of hepatic hydrothorax; it may be noted, however, that most patients (> 80%) with portal hypertension have cirrhosis. Hepatic hydrothorax has an estimated prevalence of 5 - 12% in patients with cirrhosis of the liver. It is usually right-sided (65 - 87% of reported cases) but may be left-sided or rarely bilateral[2].

Spontaneous bacterial pleuritis (SBPL), defined as the spontaneous infection of the pleural fluid in the absence of pneumonia, represents a distinct complication of hepatic hydrothorax. It has been also referred to as spontaneous bacterial empyema (SBEM). Many physicians find this term confusing because in most cases there is no evidence of pus or abscess in the thoracic cavity, and in fact, the pathogenesis, clinical features, diagnostic criteria and treatment strategy of spontaneous bacterial empyema are different from those of empyema secondary to pneumonia. Hence, most authors are of the opinion that the condition be called spontaneous bacterial pleuritis (SBPL). However, both the terms are in vogue in medical literature and used synonymously. Since the acronyms for both the terms are often confused with spontaneous bacterial peritonitis (SBP) or with sub-acute bacterial endocarditis (SBE), hence the terms have been abbreviated as SBPL (spontaneous bacterial pleuritis) and SBEM (spontaneous bacterial empyema).

Prevalence

Xiol *et al*[3], in a prospective study of 120 cirrhotic patients with pleural effusion on admission, who underwent a diagnostic pleurocentesis, found that 13% had 24 episodes of SBEM; all of them with advanced cirrhosis, and only 57% had associated SBP while in 10 of these 24 cases, SBEM was not associated with spontaneous bacterial peritonitis (SBP). Six of these 24 patients had a hydrothorax without ascites indicating that ascites is not a prerequisite for SBEM.

Chen *et al*[4] had reported that the incidence of SBEM was 2.4% in cirrhotic patients (81 cases among 3,390 cirrhotic patients) and 16% in patients with cirrhosis with hydrothorax (81 in 508 cases). Out of 98 cirrhotic patients with hydrothorax enrolled in the study by Mansour *et al*[5], 14 (14.3%) fulfilled the criteria for the diagnosis of spontaneous bacterial pleuritis.

These studies show that SBEM is a frequent complication in cirrhotic patients with hydrothorax. The incidence of SBEM when regular thoracocentesis is done in patients with hepatic hydrothorax is similar to the reported incidence of spontaneous bacterial peritonitis in patients with cirrhosis[6]. However, SBEM is frequently under-diagnosed.

Pathogenesis

Cirrhosis of liver may be considered as an immune-compromised state and is known to be associated with

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increased incidence and severity of infections[7]. The infection attributed death occurring in these patients has been estimated to be 7 - 40%. The proposed mechanisms for the increased incidence of infections in these patients include neutrophilic dysfunction, complement deficiency, deficient reticuloendothelial phagocytic action, increased tumour necrosis factor-alpha activity, and impaired antibody mediated bactericidal activity found in cirrhosis[8]. Also, patients who develop spontaneous bacterial peritonitis have been documented to have low ascites complement levels and low ascitic fluid opsonic activity. This highlights the importance of local factors in the prevention of the colonisation of ascitic fluid by pathogenic bacteria. These systemic and local factors are believed to contribute additively and are instrumental in the pathogenesis of spontaneous bacterial peritonitis. Similar mechanisms are thought to be involved in the pathogenesis of SBEM.

The exact pathogenesis of SBEM remains an enigma. The fluid aspirated from the pleural space is often similar in biochemical, cytological, and microbiological profile to that aspirated from the peritoneal cavity. The unidirectional flow of fluid from the abdomen to the chest and the evidence of pressure gradient between the two cavities have been used to explain the development of this complication[9]. SBEM was earlier believed to be a result of a direct bacterial spread from the peritoneal cavity into the pleural space via pores in the diaphragm.

However, it has been observed that in a significant proportion of the patients, the SBEM episodes were not associated with SBP. In fact, on several occasions, SBEM occurred even in the absence of ascites[3]. In such cases, other mechanisms have been speculated. It has been proposed that the underlying pathogenesis involves a transient bacteraemia that infects the pleural space. The enteric flora can reach the abdominal lymphatics and can then enter the blood stream causing a bacteraemia.

Similar to the defective local and systemic responses against infections seen in spontaneous bacterial peritonitis, pleural factors are speculated to enhance infection in these patients. The impaired opsonic activity of the pleural fluid is found to enhance bacterial translocation[10]. Sese *et al*[11] attempted to study the local factors by determining the C3, C4 and opsonic activity levels of pleural fluids, and showed that in addition to lower levels of total protein, cirrhotic patients who develop SBEM also have lower levels of C3 and pleural fluid opsonic activity.

The microorganisms isolated from pleural fluid/blood cultures of patients with SBEM in decreasing order of prevalence are *Escherichia coli*, Streptococcus spp, Enterococcus, and *Klebsiella pneumonia*[3] – these organisms are normally found in the enteric flora. Xiol *et al*[3] reported that blood cultures were positive in 4 of the ten cases of SBEM without SBP. This finding supports the hypothesis that transient bacteraemia allows these enteric flora to migrate to the pleural cavity even in the absence of ascites or SBP.

Risk factors

Only a few studies have evaluated the risk factors for developing SBEM. Sese *et al*[11] found that a low pleural fluid total protein (less than 1.0 mg/dl) and low C3 levels as well as a higher Child-Pugh score were associated with the development of a SBEM. Chen *et al*[12] also have identified that patients with SBEM had a higher Child-Pugh score, lower serum albumin, prolonged prothrombin time, lower pleural fluid protein, and higher rate of associated SBP than patients with sterile hydrothorax. Multivariate analysis revealed that pleural fluid protein level and presence of SBP were predictive factors of SBEM[12]. Patients with spontaneous bacterial pleuritis had more severe liver diseases (high MELD score), and higher rate of associated spontaneous bacterial peritonitis (SBP) and bacteraemia than patients with uncomplicated hydrothorax[5].

As there is a very good correlation between pleural C3 and total protein levels, Sese *et al*[11] recommended the use of pleural fluid total protein concentration in clinical practice to detect the patients at risk for developing SBEM.

The independent factors related to poor outcome are high MELD-Na score, initial ICU admission and initial antibiotic treatment failure[4]. In fact, high MELD-Na score may be a useful mortality predictor of SBEM in cirrhotic patients[4].

Signs and symptoms

There is no specific clinical presentation of SBEM. Fever and chills, abdominal pain, shortness of breath, chest pain, and disturbance of consciousness are recognised presentations of SBEM; it is frequently associated with few localising signs. Although ascites is usually evident at presentation, hepatic hydrothorax can present without clinically detectable ascites[3, 13].

Hence, infection of the pleural fluid may be considered in any patient with hydrothorax who develops fever, pleuritic pain, encephalopathy, or unexplained deterioration in renal function. Since the clinical manifestations and pleural fluid findings in SBEM are not as pronounced as in parapneumonic empyema, there should be a high degree of suspicion in a cirrhotic patient with hydrothorax who is hospitalised because of clinical deterioration.

Diagnosis

A high index of suspicion is essential for its diagnosis.

Whenever a diagnosis of SBEM is being considered, a chest X-ray (to rule-out pneumonia) and a thoracentesis should be performed; and a cell count from that fluid should always be sent. The diagnostic criteria for SBEM are as follows[14]:-

- Positive pleural fluid culture and a polymorphonuclear count greater than 250 cells/cu mm.
- Negative pleural fluid culture and a polymorphonuclear count greater than 500 cells/cu mm.
- No evidence of pneumonia on a chest X-ray.

Furthermore, since SBEM is probably an infection that involves a low concentration of bacteria as is SBP, conventional cultures are not sufficiently sensitive to diagnose the condition. The pleural fluid should be processed for culture in the same way as ascitic fluid is processed in a suspected case of SBP. Hence, it is recommended that pleural fluid culture should be performed by inoculating 10 ml pleural fluid into a tryptic soy broth (TSB) blood culture bottle at the patient's bedside as it has a greater sensitivity for the diagnosis of SBEM than the conventional method[3]. The reason for improved sensitivity is the immediate inoculation[15] since a TSB blood culture bottle contains an anticoagulant and opsonin inhibitor that protects bacteria from further complement- or phagocyte-mediated killing, as well as protecting the cultured volume[16]. The modified method allows the culture of a large volume of fluid and this technique is invaluable when there is a low concentration of bacteria.

It should be noted that routine pleural fluid analysis have showed limited diagnostic efficacy in the diagnosis of SBEM since lactate dehydrogenase, total protein and glucose were not reported to differ significantly between the patients with SBEM and those with non-infected effusion and it did not correlate with PMN cell count. Hence, the diagnosis of SBE should not be overlooked when these parameters are found within the expected levels.

Castellote *et al*[17] showed that the analysis of pleural fluid with a reagent strip for leukocyte esterase might represent a rapid, easy-to-use, and inexpensive tool for the diagnosis of SBEM in cirrhotic patients. However, more studies are required before its use in this scenario can be recommended.

Treatment

Since the enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*) are the major causative pathogens isolated from SBEM patients, the cornerstone of therapy is antibiotic therapy with immediate empirical use of third-generation cephalosporins as the first-line treatment[18]. The use of albumin in preventing hepatorenal syndrome is the standard of care in patients with SBP[19-21] but it has not been studied in patients with SBEM. These patients may also be placed on life-long (or until a liver transplant) prophylaxis for the prevention of SBEM (just as is done in case of SBP) with norfloxacin or ciprofloxacin[22].

Chest tube (inter-costal drainage) insertion is not indicated in the management of SBEM unless frank pus is present. Chest tube insertion can lead to renal insufficiency, prolonged drainage through the insertion site following removal, increased risk of secondary infection, and further protein loss[23-24]. Criteria for chest tube insertion are frank pus or pH <7.1 plus glucose levels <40 mg/dl.

SBP and hepatic hydrothorax are recognised indications for orthotopic liver transplantation (OLT)[25-26]. Because of SBEM's similarities and its frequent association with SBP, OLT may be used in the treatment of SBEM. Recently, Xiol *et al*[27] studied the outcome of liver transplantation in patients with hepatic hydrothorax and showed that long-term evolution was similar between patients with refractory hepatic hydrothorax or spontaneous bacterial empyema and those with non-complicated hepatic hydrothorax. Therefore, liver transplantation might be an excellent therapeutic option for patients with hepatic hydrothorax even when complicated by empyema.

Prognosis

Mortality is as high as 20% in patients with SBEM[2-3]. Just as the development of SBP is an indication for a liver transplant evaluation, the development of SBEM should prompt a referral to a liver transplant centre. According to Chen *et al*[4], SBEM is associated with a deteriorating prognosis with an estimated mortality rate of 38%. Patients are prone to recurrent bouts of spontaneous bacterial pleuritis with or without concurrent spontaneous bacterial peritonitis[14].

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"You must live in the present,
launch yourself on every wave,
find your eternity in each moment."

– HENRY DAVID THOREAU.

CASE REPORT

JIACM 2016; 17(2): 119-22

Noonan syndrome – Clinical diagnosis of a rare case

*Gouranga Santra**

Abstract

Noonan syndrome (NS) is a congenital developmental disorder characterised by facial dysmorphia, short stature, cardiac defects, and skeletal malformation. We had a 15-year-old patient, who presented with phenotypical features like short stature, low set ears, short neck, malocclusion of teeth, low posterior hair lines, widely spaced nipples, and pectus excavatum. Examination of external genitalia revealed bilateral cryptorchidism with both the testis at superficial inguinal rings. He had sexual prematurity. This case is reported for its rarity. The patient also had uncommon features like flat foot. Also, his feet were long with arachnodactyly. He had recurrent gastrointestinal and lower respiratory tract infections. No immunodeficiency disorder was detected, but he had chest wall deformity and pulmonary stenosis. Early recognition of this condition is important to avoid unnecessary costly investigations, and future complications of the disease from unawareness. Clinical features are sufficient for diagnosis in a resource-limited setting.

Key words: Facial dysmorphia, short stature, arachnodactyly, flat foot.

Introduction

Noonan syndrome (NS) is a congenital developmental disorder characterised by facial dysmorphia, short stature, cardiac defects, and skeletal malformation. We report the case of a 15-year-old boy, who presented with characteristic phenotypical features of NS along with history of recurrent lower respiratory tract and gastrointestinal infections. This case is reported for its rarity with some uncommon features and to highlight the important role of physicians in early recognition of this condition.

Case report

A 15-year-old boy born of non-consanguineous marriage presented with fever, abdominal pain and haematochezia for seven days. He also had cough and expectoration for three days. There was no history of joint pain, haematuria, vomiting, or rash. There was history of recurrent chest and gastrointestinal tract infections since childhood.

He was the second child in order of birth and was born full term at hospital. Antenatal and perinatal periods were uneventful. His elder brother and his parents were normal with no family history of tuberculosis, diabetes, or hypertension.

On examination, he was conscious, cooperative, and well oriented. He had mild pallor. His vitals were: blood pressure 100/70 mmHg; pulse 90/min, regular; temperature 100° F; respiration rate 28/min with intercostal retraction. He weighed 24 kg. His anthropometry revealed total height of 134 cm, upper segment: lower segment ratio 1: 1.6, arm span 137 cm, head circumference 47 cm, and chest circumference 58 cm. He had short stature, low set ears, short neck, grooved thick upper lip, low posterior hair lines, widely spaced nipples and pectus excavatum (Fig. 1-3). Examination of external genitalia revealed bilateral cryptorchidism with both the testis at superficial inguinal rings. He had preadolescent sexual maturity. There was associated arachnodactyly and flat foot (Fig. 4-5). His cardiovascular system examination revealed an ejection systolic murmur at the pulmonary area. Chest examination revealed presence of bronchial breath sounds at right mid-zone of chest. The patient had mild mental retardation.

His laboratory investigation revealed haemoglobin 9 gm%, total leucocytes count 11,000/cu mm, platelets 2,56,000/cu mm. His anaemia was found to be dimorphic. He had a normal coagulation profile. His stool examination revealed presence of neutrophils and blood. Serological marker for Shigella was positive. His echocardiography revealed presence of pulmonary stenosis. His chest radiograph revealed right middle-lobe consolidation and sputum culture resulted in growth of *Klebsiella pneumoniae*. A work-up for presence of any immunodeficiency was non-contributory. Total serum testosterone showed a value of 108.56 ng/dl (normal in male: 270 - 1,070 ng/dl) which suggests delayed puberty in the patient. A skeletal survey using radiographs of long bones of extremities showed normal bone age. An ear, nose, throat, and ophthalmology evaluation did not reveal any abnormality except low set ears.

He was treated with intravenous antibiotics (after culture and sensitivity). He was discharged in stable condition with haematinics and was advised regular follow-up and multidisciplinary treatment. From the phenotypic pictures, the patient was diagnosed as NS. Genetic study was not possible.

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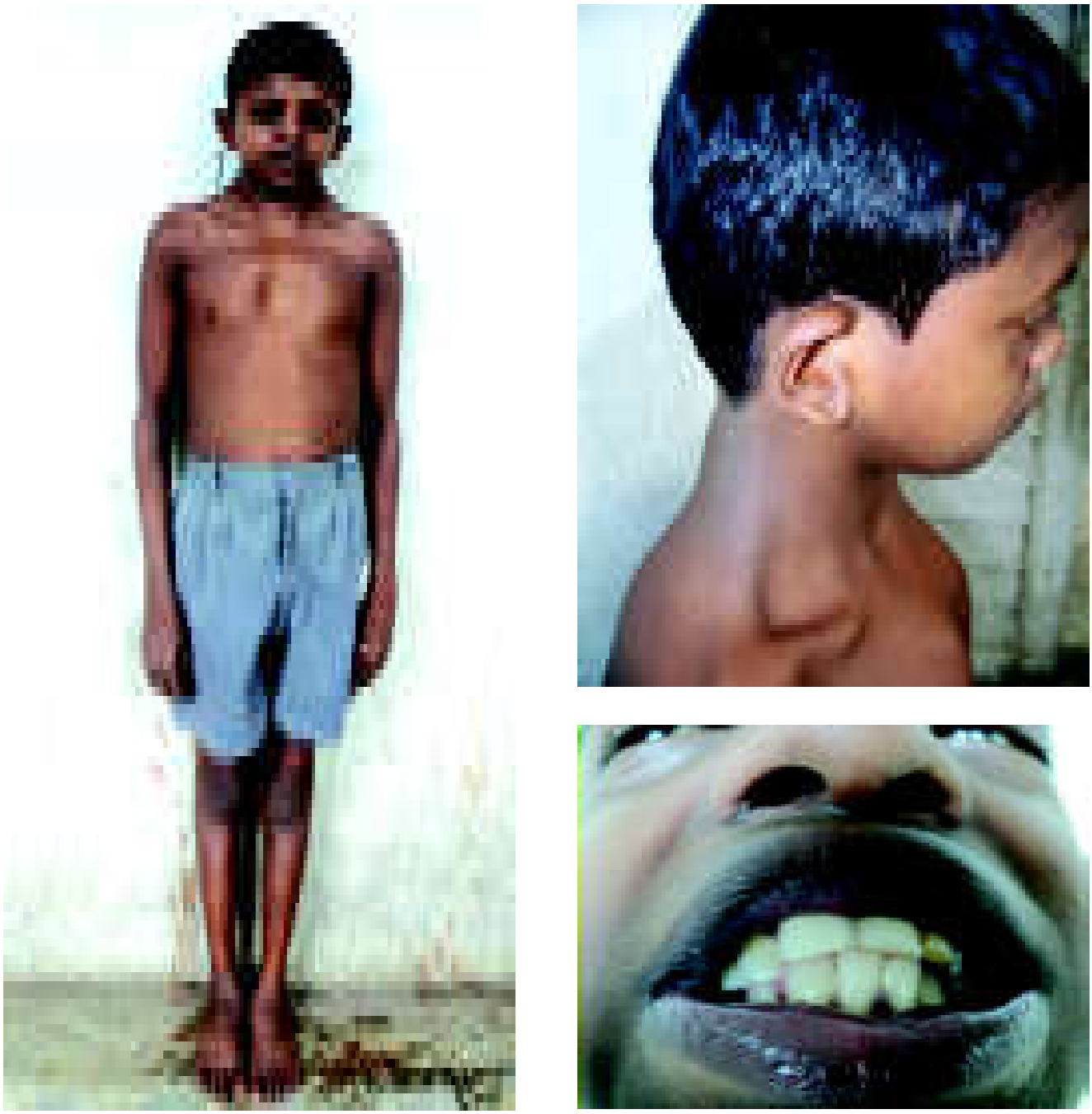

Fig. 1-3: *Photographs show a 15-year-old boy with Noonan syndrome having webbed neck, pectus excavatum, low set ears, and malocclusion of teeth.*

Discussion

Paediatrician and heart specialist Jacqueline Anne Noonan and Ehmke first described NS in 1963 in a series of patients with multiple malformations, including unusual facies and congenital heart defects. NS was also previously called as male Turner syndrome. But it occurs both in males and females. Both sporadic and autosomal dominant cases of NS with variable penetrance have been identified[1]. Missense mutations in PTPN11 gene on chromosome 12 account for approximately 50% of cases of NS, resulting in a gain of function of the non-receptor protein tyrosine phosphatase SHP-2 (src homology region 2-domain phosphatase-2) protein. Recently, mutations in *KRAS* gene have been identified in a small proportion of patients with NS[2]. Fertility in males with undescended testes may be decreased hence the mother is more frequently the transmitting parent in familial cases. The *de novo* PTPN11 mutation in sporadic NS

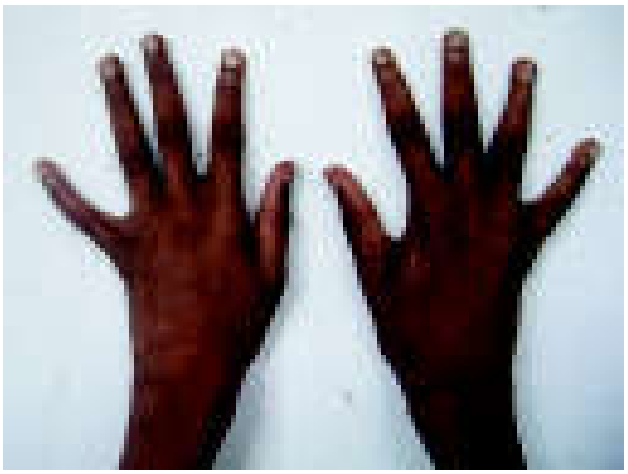

Fig. 4: *Arachnodactyly.*

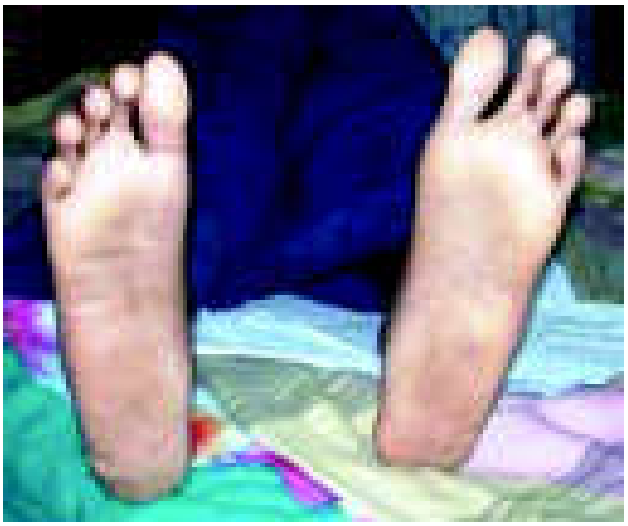

Fig. 5: *Flat foot. Feet are also long with arachnodactyly.*

cases is predominantly of paternal origin. A rare autosomal recessive form of NS is also recognised.

Main facial features of NS are hypertelorism, down-slanting palpebral fissures, ptosis, and low-set posteriorly rotated ears with a thickened helix[3]. Facial feature, in NS change with age[4]. The face becomes triangular with age. In childhood the face often appears coarse or myopathic, with thick lips, with prominent nasolabial-folds, prominent eyes, and unilateral or bilateral ptosis. The eyes are less prominent and neck appears less short in adolescent, and young adults. There may be marked webbing or prominent trapezius. Older adults often present with high anterior hair line, thick hooded eyelids, prominent nasolabial-folds and wrinkled skin. Facial features may be subtle, especially in elders[4].

The most common congenital heart defect is pulmonary stenosis with dysplastic leaflets. Other less frequent defects are hypertrophic obstructive cardiomyopathy, atrial and ventricular septal defects, persistent ductus arteriosus, etc., NS cases with a mutation in PTPN11 more often have pulmonary stenosis, while those without a mutation in PTPN11 more often have a cardiomyopathy. Our patient had pulmonary stenosis.

Pubertal delay is common, pubertal growth spurt is often reduced, and adult height gained is short. Characteristic chest deformities consist of pectus carinatum superiorly and pectus excavatum inferiorly. Thorax is broad and inter-nipple distance is large as seen in our patient. There may be associated thoracic scoliosis, cubitus valgus, radio-ulnar synostosis, clinobrachydactyly, joint hyperextensibility, and talipes equinovarus. Our patient had uncommon features like flat foot and feet were also long with arachnodactyly.

Undescended testicles associated with small penis are common. Testicular maldescent may lead to failure of spermatogenesis. Fertility is not impaired in females. Urinary tract malformations include pyelo-ureteric stenosis and/or hydronephrosis.

Increased bruising or bleeding is frequent, especially in childhood. There may be prolonged bleeding times, factor VIII, XI, and XII deficiencies, thrombocytopenia and/or platelet function defects. No correlation exists between the results of coagulation tests and history of easy bruising. Our patient had haematochezia but coagulation tests and platelet counts were normal. Acute leukaemia and myeloproliferative disorders have been described, including fatal juvenile myelomonocytic leukaemia.

Lymph vessel dysplasia, hypoplasia, or aplasia is a common problem leading to lymphoedema, pulmonary or intestinal lymphangiectasia. Pulmonary lymphatic dysplasia may even lead to chylothorax[5,6]. Features like cryptorchidism, low-set posteriorly rotated ears, hypertelorism, down-slanting palpebral fissures, and wide-spaced nipples may be due to disruption of normal tissue migration by foetal lymphoedema[7].

Abnormalities of pigmentation in NS include pigmented naevi, *cafe-au-lait* spots and lentigines. Our patient had no abnormalities of pigmentation.

Mild mental retardation can present. Behavioural problems include clumsiness, eating problems, fidgetiness, echolalia, irritability, and attention deficit. Our patient had mild mental retardation, but no behavioural problem. Ophthalmic abnormalities include strabismus, refractive errors, amblyopia, and nystagmus. Otitis media is a frequent complaint. Our patient had no ophthalmic and hearing abnormalities except low set ears.

Establishing the diagnosis of NS may be very difficult especially in adults as there is great variability in expression

and phenotypic features become less pronounced with increasing age. No confirmatory diagnostic testing for NS is available. Diagnosis of NS is still based on clinical features. Patient can be tested for mutations in the PTPN11, SOS1, or KRAS gene, however, the absence of these does not rules-out the diagnosis. Our patient could not afford the genetic tests.

There is no specific treatment. Growth hormone may be used to treat short stature. Aspirin should be avoided in NS with history of bleeding and bruising. Preoperative coagulation studies are indicated before surgery or dental work. Congenital heart lesions can be corrected by surgery. Physiotherapy and/or speech therapy should be offered if indicated. Early orchidopexy is needed to reduce the risk of malignancy and fertility problem.

Conclusion

High level of awareness is needed to diagnose Noonam syndrome as it is very rare, but with special care and counselling majority of children will grow-up and function normally in adult life. Clinical features are sufficient to diagnose NS in a resource-limited setting, especially in our country.

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"We are shaped by our thoughts;
we become what we think.
When the mind is pure,
joy follows like a shadow that never leaves."

– GAUTAM BUDDHA.

CASE REPORT

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An unusual presentation of dapsone hypersensitivity syndrome

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Abstract

Dapsone is a highly active antibacterial, antiparasitic, and anti-inflammatory agent commonly used in leprosy and in a variety of skin diseases. Dapsone can cause mild drug reaction to severe hypersensitivity reaction which may be life-threatening. We are reporting a case of a 28-year-old female who presented to us with fever, anaemia, severe cholestatic jaundice, periorbital swelling, swelling of both lower limbs, exfoliative dermatitis, difficulty in deglutition, lymphadenopathy, hepatosplenomegaly, oral and lips lesion like Stevens-Johnson syndrome, gall bladder oedema, minimal asciteis, and dilated portal vein. In this patient, dapsone was stopped and she was managed with prednisolone and hydroxyzine. The patient improved well after 6 weeks of corticosteroid therapy.

Keywords: Dapsone hypersensitivity syndrome, leprosy, corticosteroids.

Introduction

Dapsone (4, 4'-diamino-diphenyl sulfone) is a highly active antibacterial, antiparasitic and anti-inflammatory agent used in various diseases like leprosy, dermatitis herpetiformis, *Pneumocystis carinii* pneumonia, and malaria. In leprosy it is used in combination with rifampicin and clofazimine as a multidrug therapy. Most common adverse effect of dapsone is dose related, e.g., haemolytic anaemia and methaemoglobinaemia. Dapsone can cause a rare idiosyncratic reaction known as Dapsone hypersensitivity syndrome (DHS) which may be life-threatening. Here we present a case of severe dapsone hypersensitivity syndrome in a 28-year-old female being treated for leprosy in view of an anaesthetic patch over left lower arm. We managed this case with corticosteroids and antihistaminics successfully.

Case report

A 28-year-old female was provisionally diagnosed elsewhere as a case of paucibacillary leprosy in view of a solitary anaesthetic patch over the lower and lateral aspect of her left arm 8 weeks ago. She was prescribed dapsone 100 mg daily and rifampicin 600 mg monthly. The patient presented to us with fever, yellowish discoloration of the sclera and urine, itching with erythematous skin rashes, swelling of both lower limbs and face, painful lesions in the oral cavity, difficulty in swallowing, and loss of appetite for 20 days. There was no history of any drug reaction, jaundice, or anaemia in the past.

On admission, the patient's physical examination revealed that the patient was conscious, alert, and oriented. She was febrile, temperature was 100 - 102° F. Her pulse was 100/min and blood pressure was 110/60 mm Hg. Facial puffiness with periorbital oedema, angular cheilitis, pruritic erythematous macular rashes all over the body were present. She also had painful ulcerative oral lesions with hyperaemia of pharynx. There was mild pallor, moderate icterus, and moderate pitting pedal oedema. Multiple bilateral cervical and axillary lymph nodes measuring 1 - 2 cms (which were tender) were also present. Her respiratory, cardiovascular system examinations were normal. Liver was palpable 3 cm below the right costal margin and was slightly tender. Spleen was just palpable on per abdomen examination.

Laboratory investigations on admission were done which revealed Hb - 9.5 gm%, WBC - 15,200/cu mm, (polymorphs - 75%, lymphocytes - 20%, eosinophils - 5%), platelets - 2,82,000/cu mm. Serum bilirubin was 14.3 mg/dl (direct - 10.8 mg/dl, indirect - 3.5 mg/dl), SGOT - 51 U/L, SGPT - 130 U/L, ALP - 554 U/L. Serum protein was 7.0 gm/dl (albumin - 3.5 gm/dl, globulin - 3.5 gm/dl). PT - 19.2 secs, INR - 1.6. Blood urea - 46 mg/dl, sr. creatinine - 0.4 mg/dl.

Her HBsAg, anti-HCV, anti-HAV, anti-HEV, HIV, and ANA were negative. Also malarial antigen, IgM typhidot and blood cultures were negative. Urine routine was normal. Slit skin smear of the anaesthetic patch was positive for borderline tuberculoid (BT) leprosy. Her lymph node FNAC was done which showed reactive lymphadenitis.

Ultrasonography revealed: liver enlarged in size and echotexture hypoechoic suggestive of hepatits, with gall bladder oedema; spleen was also enlarged. There was minimal asciteis, multiple portal and peripancreatic lymph nodes were present, portal vein was dilated. Chest X-ray was normal.

On the basis of history, clinical and laboratory examination, the patient was diagnosed as a case of dapsone hypersensitivity syndrome (DHS). Dapsone was

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discontinued. The patient was initially given iv corticosteroids (hydrocortisone 100 mg), antihistaminic, and antibiotics. After the first 3 days, the patient was shifted onto oral steroids (40 mg prednisolone). The antibiotics and antihistaminics were given for 7 days and were then stopped. Oral corticosteroid was continued for 6 weeks with tapering down of the dose. Patient improved gradually during this period with the most dramatic improvement in symptoms of painful deglutition, facial puffiness and swelling of limbs during the first week. Clofazimine was started for boderline tuberculoid (BT) leprosy .

Discussion

Dapsone is a sulfone class drug related chemically to sulfonamide. Its antibacterial action is by inhibiting bacterial synthesis of dihydrofolic acid via competition with para aminobenzoate for the active site of dihydropteroate synthatase. Dapsone is being used in leprosy since 1950. Dapsone is also used in dermatitis herpetiformis, *Pneumocystis carinii* pneumonia, immune thrombocytopenic purpura, toxoplasmosis, and malaria. On oral administration, it is absorbed completely in the gut and is widely distributed in the body. It is 70% plasma protein bound and concentrated in the muscle, liver, and kidney. Dapsone is metabolised through N-acetylation and N-hydroxylation. It is excreted mainly by the kidney. It is also excreted in the bile, but is reabsorbed from the intestine, i.e., enterohepatic circulation. Its elimination half life is > 24 hours. Dapsone is one of the drugs which causes hypersensitivity reaction; others are phenytoin, carbamazepine, allopurinol, minocycline, etc.

Dapsone hypersensitivity syndrome (DHS) usually occurs 4 - 6 weeks after initiation of therapy. Its incidence is understood to be increased due to WHO-MDT therapy. According to Rao and Laxmi, the incidence of DHS is 1 - 4%. DHS usually presents as high grade fever, malaise, desquamation of skin, lymphadenopathy, eosinophilia, hepatitis, anaemia, hepatosplenomegaly. In our case, besides these presentations, minimal ascites, peripancreatic and portal lymph node and dilated portal vein were also present. DHS is considered a manifestation of DRESS (Drug reaction with eosinophilia and systemic symptoms) syndrome. Liver involvement is usually hepatocellular and cholestatic. Cholangitis has also been reported in a case of DHS. Cutaneous manifestation of DHS is almost always present while other features may vary. According to Richardus and Smith, a true diagnosis of DHS should be made on following criteria:-

- Symptoms appeared within 8 weeks of starting therapy and resolved after withdrawal of drugs.
- Symptoms not attributable to other drugs used simultaneously.
- Symptoms unrelated to leprosy or any underlying diseases.

Pathogenesis of DHS is not established clearly but it is presumed that hydroxylated metabolites are important in the pathogenesis. A reduction in N-hydroxylation enzyme levels or activity results in decreased total clearance of dapsone. Ageing and pre-existing liver disease may offer protection against adverse effects because decreased enzyme activity then decreased production of toxic metabolites. Allday and Barnes reported that pathogenesis of DHS was due to hypersensitivity because there was an interval of 4 - 6 weeks from the starting of therapy in almost all case of DHS.

Diagnosis of DHS is made on the basis of history, clinical and laboratory findings. If the facility is available, lymphocyte stimulation test with dapsone may be done. Oral challenge test with dapsone is dangerous, and is therefore not recommended.

Management of DHS consists of withdrawal of Dapsone and supportive measures. Usually DHS is self-limiting. Systemic corticosteroids are used for the treatment, i.e., prednisolone in a dose of 1 mg/kg. No controlled trial has been performed for the evaluation of its effectiveness. Anecdotal experience has resulted in the widespread use of corticosteroids in DHS. Corticosteroid is tapered in 6 weeks because dapsone is present for upto 35 days in organs via protein bonding and enterohepatic circulation.

Mortality as high as 12 - 23% has been reported in severe DHS, so prompt diagnosis and treatment is essential. Physician, dermatologist and leprologist should be aware of this condition if treating any condition using dapsone.

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CASE REPORT

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Sudden bilateral vision loss in a patient of fibrous dysplasia due to ruptured sphenoid sinus mucocoele

Mayank Arora, Saurabh Gupta*, Shafali Nandwani*, SK Virmani*, Moneet Agarwal*, Avinash Munshi**

Abstract

Fibrous dysplasia is a developmental anomaly of bone, often affecting the facial bones. We present a case of fibrous dysplasia with bilateral sudden loss of vision. MRI showed ruptured sphenoid sinus mucocoele compressing the optic nerves. Immediate surgical exploration and decompression restored the vision.

Keywords: Fibrous dysplasia, mucocoele, vision loss, optic nerve decompression.

Introduction

Fibrous dysplasia is a developmental anomaly of bones, often affecting the facial bones[1]. It is caused by a post-zygotic, activating mutations of the GNAS gene leading to replacement of normal marrow and bone by fibrous tissue and woven bone[2]. Involvement of the craniofacial bones can produce visual loss, proptosis, diplopia, and epiphora[3]. We present a case of sudden onset bilateral vision loss in a patient of fibrous dysplasia caused by sphenoid sinus mucocoele in which immediate decompression of the optic nerve restored the vision.

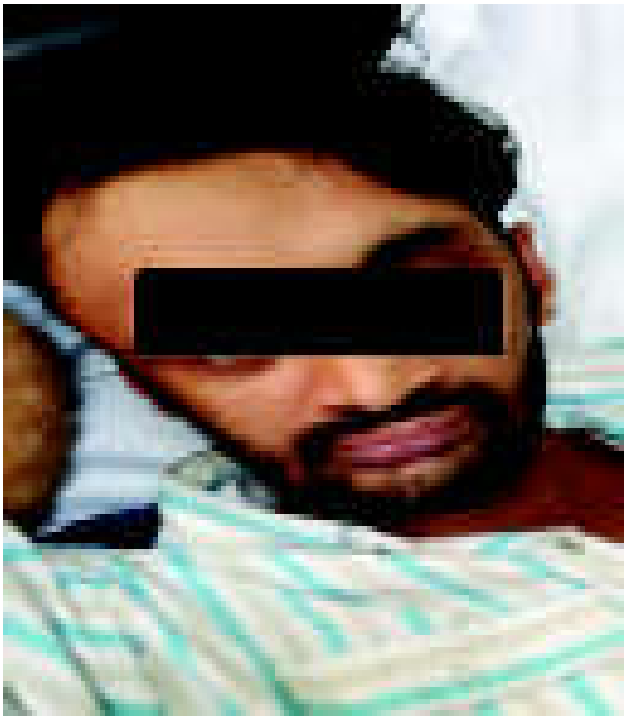

Fig. 1: *Image showing right frontal swelling in a 32-year-old male.*

Case report

A 32-year-old male was brought to the hospital with history of headache since three days and bilateral vision loss from last 4 hours. There was no complaint related to vision in the past. General physical examination revealed an asymmetric skull deformity with a bony swelling over the right frontal bone. There was 7 cm shortening of the right lower limb. Visual acuity of perception of light in the right eye and finger counting at 1 metre in the left eye was found. Fundus examination revealed minimal temporal pallor of optic discs bilaterally. CT face and MRI brain were done besides the routine investigations. CT face revealed an expansile calvarial lesion more on the right side of the frontal bone, right orbital plate, right parietal bone and occipital bone with features consistent with polyostotic fibrous dysplasia. MRI scan revealed a sphenoid sinus mucocoele extending into the

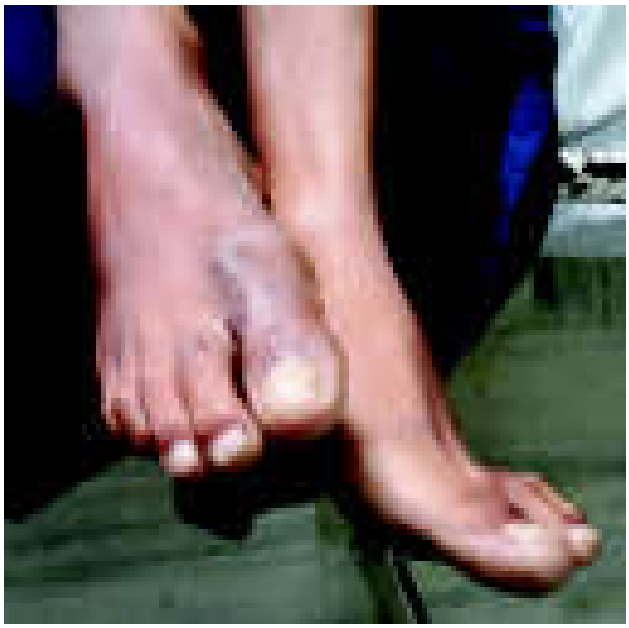

Fig. 2: *Image showing relative right lower limb shortening.*

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clivus with air-fluid level suggestive of ruptured mucocoele of sphenoid sinus. A diagnosis of ruptured sphenoid sinus mucocoele was made and immediate decompression was done on the same day via transethmoid approach. The patient gradually regained his vision with visual acuity of 6/9 bilateral eyes two weeks after the surgery.

Discussion

Craniofacial fibrous dysplasia associated with acute vision loss has been reported with mucocoeles, haemorrhage, and haemorrhagic cysts, as well as with fibrous dysplasia alone when the optic canal is involved[3]. Several cases of

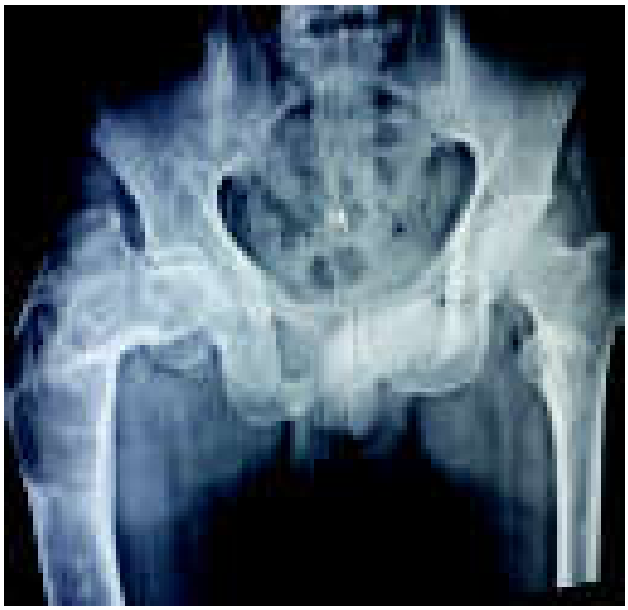

Fig. 3: *X-ray pelvis with both hips and proximal femur:-*

- *Expanded and deformed right proximal femur with cystic areas having sclerotic ring and ground glass appearance. This deformity has been called Shepherd Crook deformity.*
- *Multiple bony involvement is consistent with polyostotic variety of fibrous dysplasia.*

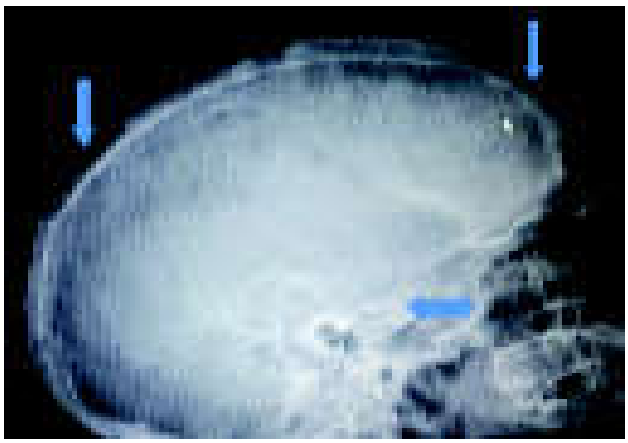

Fig. 4: *X-ray skull lateral view:-*

- *Outward expansion of the outer table with maintained inner table and ground glass density differentiates from the Paget's disease; however, the age also excludes the Paget's disease.*
- *The sphenoid sinus is also expanded.*

Fig. 5: *Axial cut 3D fiesta.*

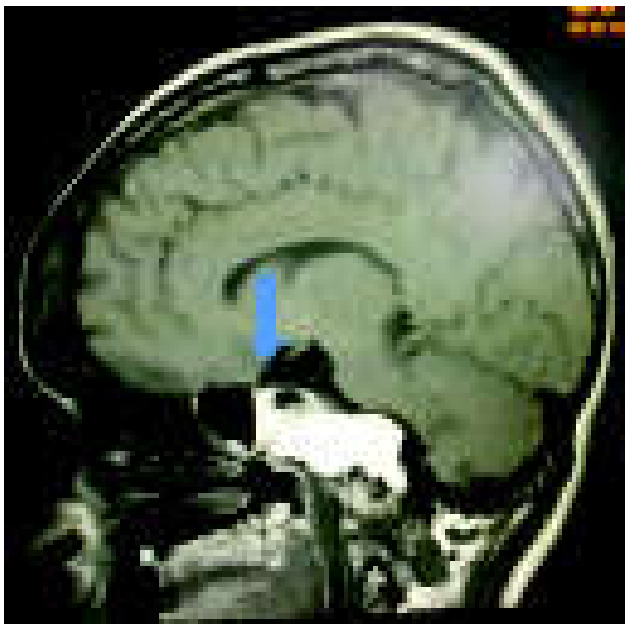

Fig. 6: *Plain T1 sagittal section:-*

- *Fiesta (highly T2 weighted thin section) and para SAG T1 shows hyperintense signal of the collection on both sequences in the expanded sphenoid sinus with air-fluid level s/o mucocoele of the sphenoid. Fluid level is likely due to recent transnasal surgery or spontaneous rupture.*
- *Axial cuts shows mucocoele reaching upto the orbital apex on both sides and para-sagittal TI shows mucocoele reaching upto the optic chiasma.*

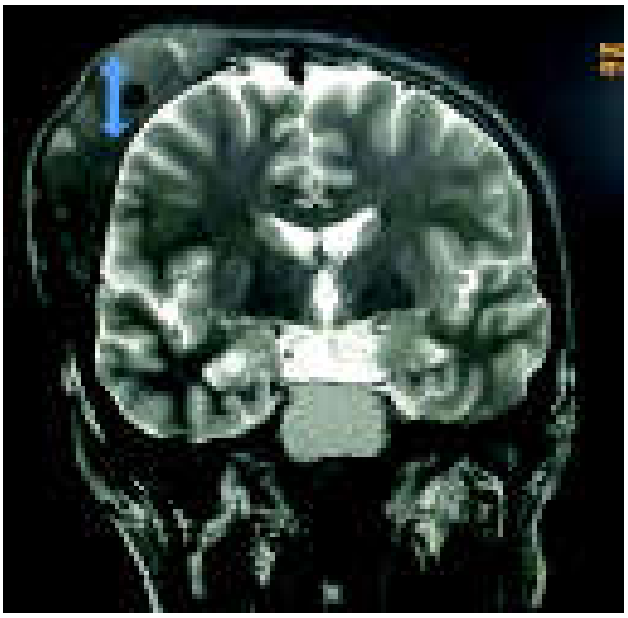

Fig. 7: *T2 coronal section:-*

- *Showing expansion of the right side of the frontal bone with T2 heterogeneous hyperintense signal. Also note maintained inner table outline.*

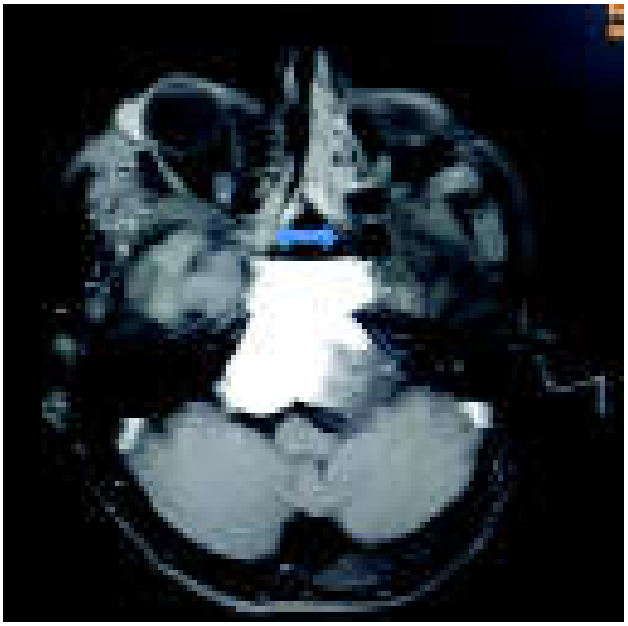

Fig. 8: *Contrast T1 axial view:-*

- *T1 post-contrast showing mild enhancement of the anterior wall of the mucocoele marked by double arrow.*

sudden acute loss of vision caused by sphenoid mucocoele have been reported in the literature[4,5]. Weissman *et al* (1990) reported a case of fibrous dysplasia with sudden loss of vision. Radiological investigations revealed mucocoele at the orbital apex and optic canal compromise by bony proliferation. Surgical excision of the cyst and debulking of the fibrous dysplasia improved the vision[1]. Dowler *et al*

Fig. 9: *3D CT scan of face:-*

- *Expanded right side of frontal bone deforming the roof of orbit.*
- *This has been described as facial asymmetry in the literature.*

(1995) reported a case of sudden bilateral loss of vision in Albright's syndrome which was treated with surgical decompression with resultant improvement in vision. The patient attained vision of 6/9 in each eye one year after surgery[5]. Papadopoulas *et al* (1998) reported two cases of acute reversible visual loss in which one patient had a sphenoid sinus mucocoele compressing the optic chiasma and the other had optic nerve narrowed by dysplastic bone. In both cases optic nerve decompression restored vision to normal. In our case it was the prompt diagnosis and immediate surgical decompression which resulted in regaining the vision loss.

Conclusion

Prompt diagnosis and immediate surgical decompression can be sight saving in cases of sphenoid mucocoeles associated with vision loss.

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CASE REPORT

JIACM 2016; 17(2): 128-29

Cutaneous presentation of chronic lymphocytic leukaemia

Kavita Paul, Harbans L Kazal**, Jasmine Kaur****

Abstract

Cutaneous manifestations of CLL are present in 4 - 50% of patients. In this report we describe a 45-year-old male patient who presented with nodular swellings over face and hands with generalised lymphadenopathy. His peripheral blood smear and bone narrow examination confirmed the diagnosis of CLL. His skin biopsy taken from nodular swelling on face showed abnormal lymphocytes infiltrating the dermis. Leukaemia cutis is a sign of poor prognosis in CLL.

Introduction

Chronic lymphocytic leukaemia (CLL) is a neoplastic disease characterised by the accumulation of small, mature-appearing lymphocytes in the blood, marrow, and lymphoid tissues. CLL is the most common leukaemia of adults in the Western world. There are about 15,000 new cases of CLL each year in the United States. The median age at diagnosis is 60 years, and there is a 2: 1 male predominance. More than 25 per cent of patients are asymptomatic at diagnosis. Such patients generally are detected because of the discovery of nontender lymphadenopathy or an unexplained absolute lymphocytosis. Otherwise, patients may have only mild symptoms of reduced exercise tolerance, fatigue, or malaise.

Case report

A 45-year-old male patient, presented with complaints of skin rash and nodular swellings over face, neck and forearms since the last 4 months. History of decreased appetite and weight loss was also present, since that time. The rash and nodular swellings were present only on the exposed parts of the body i.e., face, neck and forearms and were associated with rednesss and itching . General physical examination revealed generalised lymphadenopathy including cervical, inguinal, and axillary lymph nodes. There were erythematous papules, nodules, and plaques on the face, neck, and dorsum of hands. Per abdominal examination showed the presence of hepatosplenomegy. Routine investigations including complete blood counts showed Hb levels of 9.6 g/dl, TLC of 160,000/cu mm, DLC with 94% lymphocytes, 4% of promyelocytes, 1% of neutrophils and 1% basophils, and platelets 68,000/cu mm. His peripheral blood film showed the normocytic normochromic anaemia with marked leucocytosis and few promyelocytes.

Bone marrow examination done from posterior superior iliac crest showed hypercellular marrow with depressed erythropoiesis, and myelopoiesis. There was marked increase in (80%) in lymphoid cells with predominant population of monomorphic cells. Individual cell was having round nuclei, mature clumped chromatin, mild-to-scanty cell cytoplasm and it confirmed the diagnosis of chronic lymphocytic leukaemia. Skin biopsy was taken from face and it showed abnormal lymphocytes infiltrating the dermis and subcutaneous tissue. This suggested skin infiltration of CLL.

Discussion

The prevalence of cutaneous manifestations in CLL ranges between 4 - 50% of cases and may represent the first sign

Fig. 1: *Picture showing nodular swelling on face.*

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of the disease[1,2]. The cutaneous lesions can be classified into specific lesions or leukaemia cutis, and non-specific lesions. Leukaemia cutis (4 - 20 % of all cases) is defined by the skin infiltration by leukaemic lymphocytes.

Fig. 2: *Picture showing infiltration of hands.*

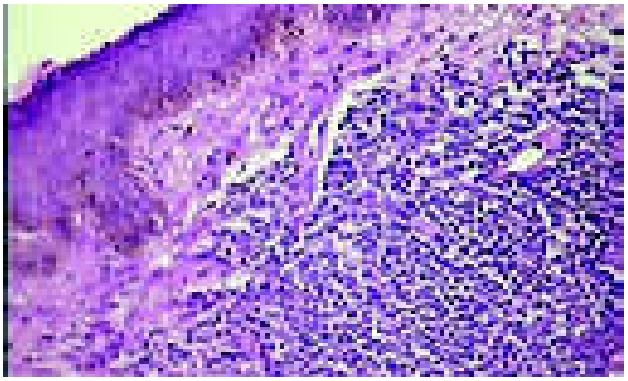

Fig. 3: *H and E staining of skin biopsy showing abnormal lymphocytes infiltrating the dermis.*

It has also been described that the infiltration by leukaemic cells may occur in the site of previous scars, herpes simplex infection, traumas, and larva migrans. Occasionally intense specific leukaemic infiltrates have been reported within the inflammatory infiltrate of cutaneous malignant neoplasms in patients with CLL.

Cutaneous CLL deposits develop most commonly on the face, but localised lesions at other sites as well as generalised disease may occur. Lesions may variably manifest as macules, papules, plaques, nodules, tumours, ulcers, or blisters.

The mechanism of cutaneous infiltration of leukaemic cells is not well understood. It is generally accepted that the migration of lymphocytes from the vasculature to the dermis in CLL is mediated by interaction between intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function associated antigen-1[3].

Kaddu *et al* investigated 54 skin biopsy specimens of specific skin infiltrates from 27 B-cell CLL patients and pointed out that the prognosis of the patients with leukaemia cutis in B cell-CLL was related to their histopathologic characteristics and the presence of leukaemia cutis is a sign of a poor prognosis; however, the prognosis of B-cell- CLL patients with leukaemia cutis has been reported to be longer than that of patients with any other type of leukaemia with leukaemia cutis[4,5].

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"The person who has lived the most is not the one with the most years,
But the one with the richest experiences."

– Jean-Jacques Rousseau.

CASE REPORT

JIACM 2016; 17(2): 130-32

Intradural extramedullary tuberculoma causing compressive myelopathy in a patient with human immunodeficiency virus infection

SB Devi, N Robinson**, R Akshay***, P Obang***, K Jaya****

Abstract

A 43-year-old man with human immunodeficiency virus (HIV) infection on anti-retroviral therapy (ART) developed acute spastic paraplegia and sensory disturbances. Cerebrospinal fluid (CSF) analysis and Interferon gamma release assay (IGRA) were suggestive of tubercular meningitis. Magnetic resonance imaging revealed an intradural extramedullary long segmental mass at the C7-T1 vertebrae level. Intradural extramedullary tuberculoma of the spinal cord is a rare complication of tuberculous meningitis which can lead to neurological deficits such as paraplegia, and require prompt treatment as they respond to conventional antituberculous therapy.

Introduction

Tuberculosis is the most common opportunistic infection among patients suffering from HIV-AIDS in India, with the prevalence of co-infection being around 5 - 10% according to NACO in 2008. Patients infected with HIV are especially prone to tubercular infection or reactivation of a latent TB infection when their CD4 cell count falls below 350 cells/cu mm, and tuberculosis occurs at extra-pulmonary sites in upto 30 - 40% of these patients[1]. Central nervous system involvement in patients with tuberculosis is estimated to be approximately 10% with tuberculous meningitis being the most common manifestation[2-4]. Spinal tuberculoma is also an extrapulmonary manifestation of tuberculosis involving the central nervous system, and is characterised as extradural, intradural extramedullary, or intradural according to its location. Intradural extramedullary tuberculoma is extremely rare and only 30 cases have been reported in the literature[4-8].

We describe a case of intradural, extramedullary tuberculoma meningioma as a complication of tuberculous meningitis in a patient with human immunodeficiency virus (HIV) infection.

Case report

A 43-year-old male with known HIV positive status, who was on an ART regimen comprising of tenofovir, lamivudine and efavirenz, with the latest CD4 cell count of 96 cells/cu mm, and HIV RNA of 3,90,000 copies/ml, presented with acute progressive spastic paraplegia following low grade fever since 15 days. He developed complete inability to move his lower limbs, as well as inability to turn side-to-side when lying down, with in a period of 2 days . He was also found to have loss of all sensory modalities below the level of 3rd thoracic segment (T3). He also had simultaneous atonic bladder and loss of bowel control. CSF analysis revealed elevated proteins (184 mg%), cell count (200 cells/cu mm with 80% lymphocytic predominance) and adenosine deaminase (ADA) levels (23.3 U/L) while glucose level was low (30 mg%) suggestive of tubercular meningitis. Acid-fast staining was negative in the CSF. Interferon gamma release assay (IGRA) performed with quantiferon TB gold test was positive. Spinal MRI showed a well-defined, long, segmentally located mass measuring 2 x 1 x 0.8 cms in the intradural, extramedullary space of the posterior spinal canal at C7-T1 vertebral level with severe lateral cord compression and displacement. It was isointense on T1 weighted and moderately hyperintense on T2 weighted image and showed enhancement with gadolinium contrast (Fig. 1 and 2). The tests for other CNS opportunistic infections such as cryptococcus, toxoplasma gondii and cytomegalovirus were negative. A neurosurgical consultation was taken, but resection or biopsy of the mass was not performed because of the patient's poor general clinical condition. He was initiated on ATT and discharged. On follow-up after 1 month his neurological deficits were found to be improving with definite improvement in power of the lower limbs and regaining of bowel and bladder control.

Discussion

Spinal involvement in tuberculosis is classified into four categories: Pott's spine, nonosseous spinal tuberculoma, tuberculous arachnoiditis, and tuberculous meningitis. Intradural spinal tuberculomas are estimated to be composed of only 2% to 5% of central nervous system tuberculomas[2,4-6].

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Compton and Dorsch reported 11 cases of intradural extramedullary tuberculoma in 1984. Since then, there have been 19 more cases reported in medical literature[2,4,6-8]. All cases, except for 4, initially presented with tuberculous

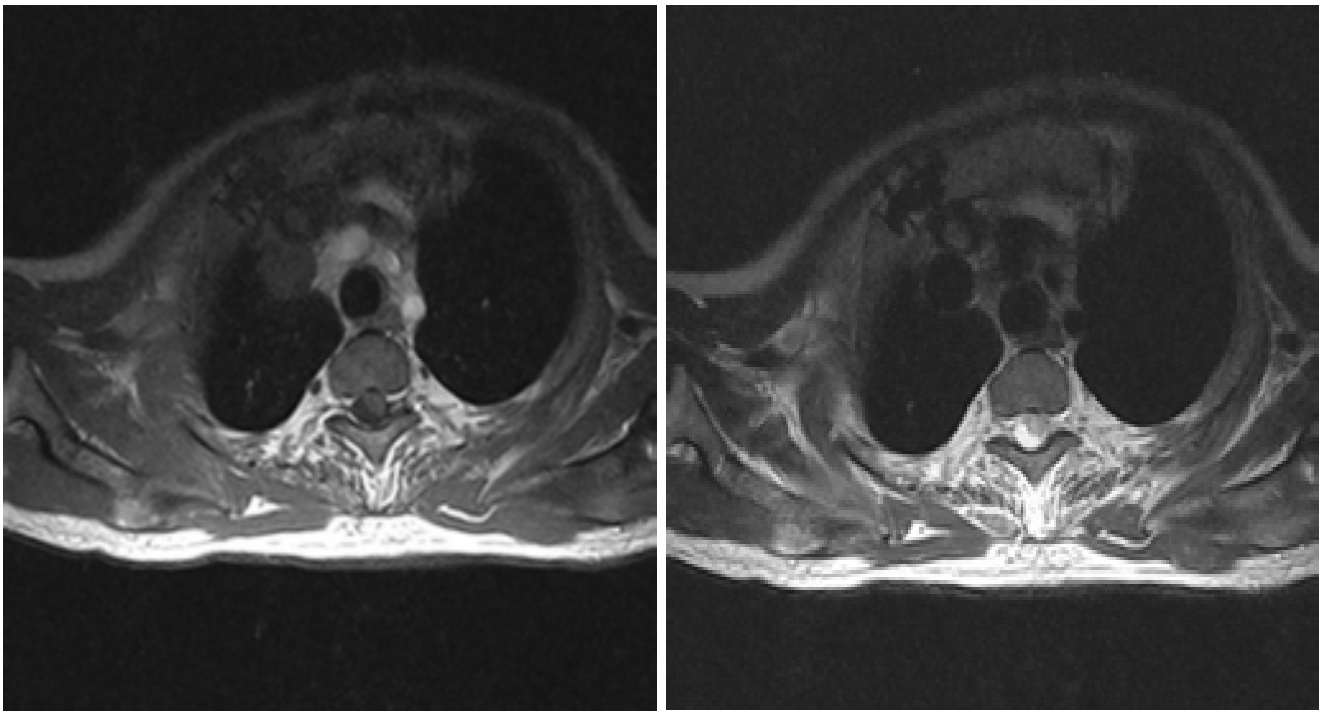

Fig. 1: *Cross-section of thoracic spine showing compressive intradural mass showing enhancement post-contrast.*

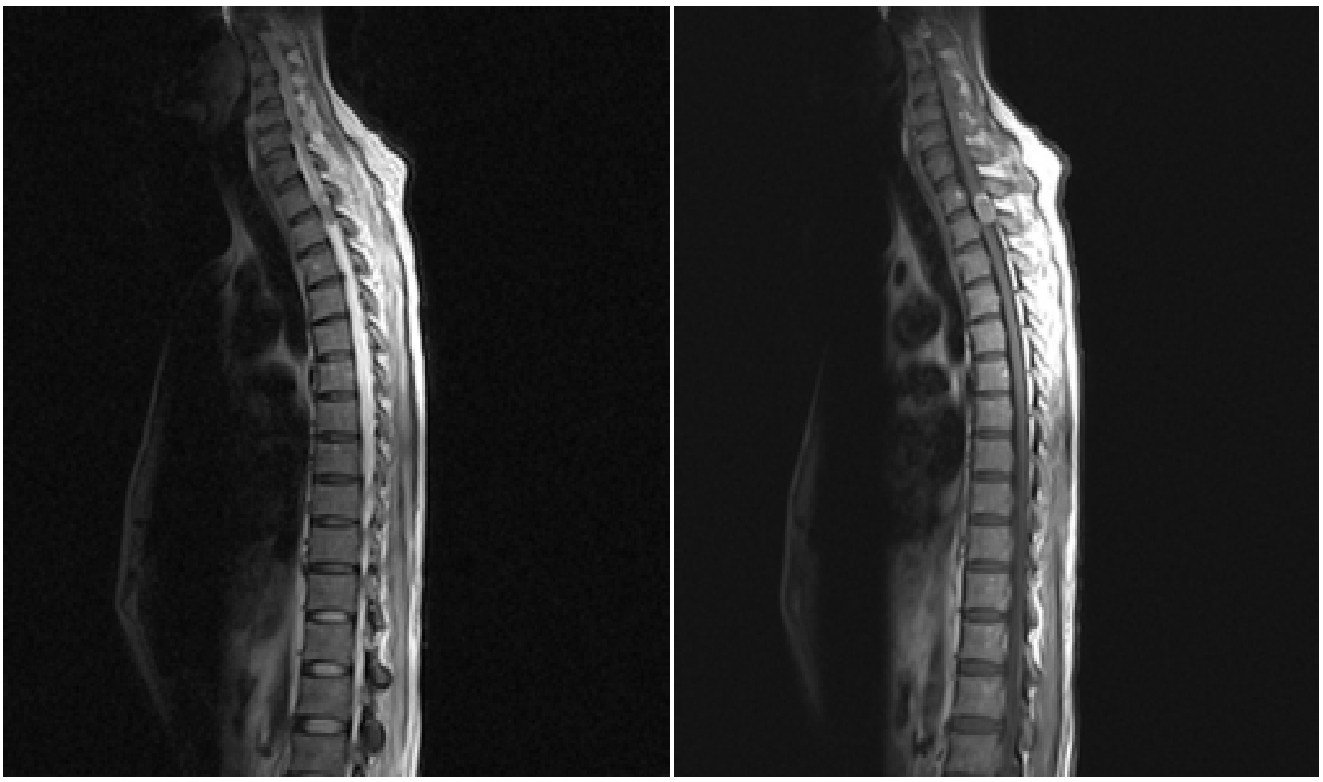

Fig. 2: *Longitudinal view of the intradural mass before and after contrast.*

meningitis. Most case reviews involved the thoracic spine[2,4,6-8]. The diagnostic method is generally histopathology, even though AFB cultures from the granulomas were positive in only one of the reported cases[8]. A myelogram can be helpful but MRI is the diagnostic procedure of choice.

The prognosis for neurological improvement is good with a prompt surgical excison and appropriate antituberculous medication[4,5,7]. Although intramedullary tuberculoma can be treated with medication alone, a surgical intervention is essential when intradural extramedullary tuberculoma causes compression of spinal cord.

En plaque meningioma can also present with thoracic spinal cord and nerve root compression[2]. The differential diagnosis between tuberculous patchy meningitis and meningioma in the form of plaque is difficult without obtaining a biopsy specimen. Since this patient with HIV and low CD4 cell count had CSF features suggestive of TB meningitis and had a positive IGRA test, and his clinical condition improved after initiation of ATT, the intradural lesion was most likely an intradural tuberculoma, although a biopsy could not be performed for confirmation.

In conclusion, intradural extramedullary tuberculoma can occur in tuberculous meningitis. Although quite rare, intradural extramedullary tuberculomas should be considered in a differential diagnosis for a patient with acute spastic paraplegia.

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"It is health that is real wealth and not pieces of gold and silver."

– Mahatma Gandhi.

CASE REPORT

JIACM 2016; 17(2): 133-34

Spinocerebellar ataxia type-2 presenting with signs of amyotrophy

Nitya Nand, Sameer Aggarwal**, Virender Chauhan***, Nisha Batra****

Abstract

Spinocerebellar ataxia (SCA) is a progressive, degenerative, genetic disease involving cerebellum and its connections with multiple subtypes. It is an uncommon disease. We report a case of a 32-year-old male who presented with bilateral cerebellar signs and amyotrophy with family history suggestive of an autosomal dominant pattern of inheritance. He was found to have spinocerebellar ataxia type 2 on genetic testing.

Keywords: Autosomal dominant, spinocerebellar ataxia, inherited ataxia.

Introduction

Spinocerebellar ataxia (SCA) has a worldwide distribution, but some cases are more prevalent in one region than the other. SCA 2, SCA 3, and SCA 6 appear to be the most common and together account for nearly half of all families worldwide. SCA-2 is typically the most common among the SCAs in India[1], and stands as the next most common SCA after SCA-3 worldwide. Spinocerebellar ataxia type II (SCA 2) is characterised by gait and limb ataxia, dysarthria, ophtalmoplegia, and polyneuropathy[2]. Extrapyramidal system signs and dementia are observed at late clinical stages. SCA-2 is caused by an expanded (CAG) trinucleotide repeat on the chromosome 12 resulting in production of abnormal protein called ataxin-2. The symptoms usually begin in the third or fourth decade of life.

In this paper we report about a family which was affected by SCA for three generations.

Case summary

A 32-year-old male, resident of Haryana, born out of nonconsanguineous marriage, with normal birth and developmental history, presented with imbalance while walking since 10 years, with a tendency to reel and fall in an unpredictable direction, along with in coordination of both hands for same duration, causing difficulty in writing, eating, and operating appliances. The above symptoms were progressive in nature. There was a history of involuntary violent movements of lower limbs during sleep. His medical history was otherwise unremarkable. There was no relevant past history. There was no history of exposure to alcohol, drugs, or toxins. There was history of similar symptoms in his grandmother and her brothers, his father and his uncle and daughter of his uncle, suggestive of autosomal dominant inheritance (Fig. 1), however, this could not be confirmed by molecular studies.

On examination: He had normal vitals and general physical examination. His mental status was normal. Speech was dysarthric (scanning). He had lid retraction in the right eye and slow horizontal saccades; however, rest all cranial nerves examination was normal. No nystagmus was observed and both fundi were normal. Motor system examination revealed reduced bulk and atrophy of hands, power was 4/5 in all muscle groups, with decreased tone. Fasciculations, were present in tongue and all limbs. Superficial and deep tendon reflexes were absent in all four limbs, and plantars were flexor bilaterally. Joint position and vibration sense was reduced globally. There were cerebellar signs in both upper and lower limbs with ataxic gait.

Complete haemogram, liver function test, renal function test, thyroid function tests were normal. Serum Vitamin B12, folate levels were normal. No Kayser-Fleischer rings were seen on slit lamp examination. Chest X-ray and electrocardiogram were normal. Magnetic resonance imaging the brain revealed olivo-ponto-cerebellar atrophy. Gene analysis revealed SCA-2 positivity. Nerve conduction studies revealed decrease in conduction velocity and amplitude of bilateral tibial, peroneal, and ulnar nerves. Electromyography showed that bilateral tibialis anterior, bilateral vastus medialis muscles showed 50 - 60% recruitment, mildly decreased amplitude while bilateral deltoid shows 70 - 80% and recruitment but bilateral abductor digiti mininimi shows 20 - 30% recruitment and severly decreased amplitude, while Ist dorsal interossei shows 5 - 10% recruitment s/o neuromyopathy.

Discussion

Spinocerebellar ataxia type 2 represents a genetically defined neurodegenerative disorder characterised by autosomal dominant inheritance and progressive cerebellar ataxia, combined with slow saccades and

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sensorimotor neuropathy. The neuropathology comprises olivo-ponto-cerebellar atrophy (OPCA) with axonopathy of posterior columns, spinocerebellar tracts, and peripheral nerves. The underlying mutation of SCA-2 consists of unstable expansion of the trinucleotide repeat (CAG) 8 CAA (CAG) 4 CAA (CAG) 8 within the ATXN-2 gene exon 1 located on chromosome 12q24.1. This repeat encodes a polyglutamine (polyQ) tract in the protein ataxin-2. In normal individuals, the trinucleotide repeat length varies and contains between 13 and 27 units. Affected SCA-2 individuals have 32 or more CAG repeats, with 37 to 39 repeats representing the most frequent pathologic expansion. The expanded alleles have lost interrupting CAA-triplets, a factor thought to promote the length instability. Currently, the function of ATXN-2 is not clear, but several lines of evidence evoke its involvement in RNA metabolism. ATXN-2 and its orthologues in other organisms relocalise during periods of cellular stress to mRNP granules where mRNA is stored during translation repression, promote the formation of these stress granules and inhibit cell growth. Mean age at onset is typically in the fourth decade. Anticipation may occur, particularly with paternal transmission; those affected individuals generally have longer CAG repeat lengths and earlier symptom onset age. SCA-2 has been reported in various ethnicities including Cuban, Indian, Italian, Mexican, South African, and Spanish. Besides ataxia, SCA-2 features may include slowed saccades (which may progress to ophthalmoparesis), brisk deep tendon reflexes (which may progress to areflexia), peripheral neuropathy, dementia, myoclonus, dystonia, chorea, and levodopa-responsive Parkinsonism. Sleep disturbances are frequent complaints of SCA-2 patients and their relatives. The most prominent sleep disorders are restless legs syndrome. Milder phenotypes with less prominent ataxia, neuropathy, dystonia, and myoclonus but greater Parkinsonian features have been associated with shorter CAG repeat expansions.

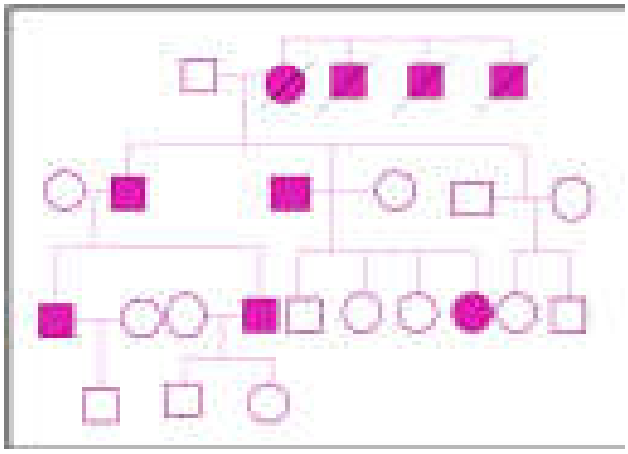

Fig. 1: *Autosomal dominant pattern of inheritance in three generations.*

In the reported family, affected members had cerebellar dysfunction of variable degree. Most patients began with dysarthria and gait ataxia. As the disease progressed, limb ataxia became more pronounced. Family members who were examined showed slowness of horizontal saccadic eye movements to a variable degree and limb and gait ataxia, but none of the family members were affected so early and with severe degree of impairement as the presenting case. Secondly, none of the family members have the fasciculations and features of amyotrophy except for the presenting case. This could be attributed to the phenomenon of anticipation and different degrees of expansion in maternal or paternal transmission. The clinical suspicion of SCA type 2 was confirmed by genetic study in two members (patient and his uncle). Testing for dominant ataxias should be included in the evaluation of patients with ataxia, especially in cases with a positive family history for spinocerebellar ataxia. New gene locuses which are linked to SCAs, are discovered every other day. Genetic study is significant in defining SCA types which are common in our country.

Conclusions

Although SCA-2 is the most common SCA in India, due to the multi-ethnicity and multi-religious pattern of society, other uncommon SCAs may also be detected in presently unreported populations of the country. The clinical phenotype suggestive of a particular SCA type may sometimes vary even in the same family despite having same genotype.

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CASE REPORT

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Left bundle branch block – A rare hyperkalaemic ECG manifestation

*M Venkata Madhav**, G Anvesh*, KV Seshaiah**, G Eswar***, Ajith Mohammad**

Abstract

A young female patient with chronic kidney disease was brought to our emergency medical department with symptoms of pain in chest, abdomen, and vomitings. Emergency laboratory values were potassium (K^+)7.7 mEq/l, creatinine 9.1 mg/dl, and ECG showed left bundle branch block (LBBB) pattern with left axis deviation, in addition to tall T-waves and ST changes. Among hyperkalaemic ECG alterations, LBBB is rare which is reported in our case. ECG manifestations in hyperkalaemia and their correlation with serum K^+ levels are discussed and the literature is reviewed.

Key words: Electrocardiogram, hyperkalaemia, left bundle branch block.

Introduction

Extracellular K^+ concentration is normally maintained between 4.0 - 4.5 mEq/l. Hyperkalaemia is defined as serum K^+ greater than 5.0 mEq/l. Hyperkalaemia is a common metabolic disturbance with potentially life-threatening consequences. While the incidence of hyperkalaemia in the general population is not well reported, in hospitalised patients it is 1% to 10%, with a mortality ratio of 1 per 1,000 patients[1]. ECG may provide the first evidence of hyperkalaemia, but patient-to-patient variability is high. Even though most common ECG findings in hyperkalaemia are peaked T-waves and increase in the duration of QRS complex, hyperkalaemia can cause several characteristic abnormalities that are often progressive. Among ECG abnormalities LBBB is rare, which is reported in our case. Many studies documented poor correlation between serum K^+ level and any specific ECG finding and concluded that sensitivity of ECG for diagnosis of hyperkalaemia is poor. At the same time, any ECG change in the clinical background of hyperkalaemia should be viewed as an emergency and empirical treatment initiated.

Case report

A 20-year-old female patient was brought to our emergency department with complaints of pain abdomen, vomitings, and retrosternal chest pain of acute onset. Abdominal pain and chest pain were of dull aching character and not related to any known precipitating factors. She was diagnosed as having chronic kidney disease (CKD) and was on maintenance haemodialysis for the past 3 months. Her past history including birth and childhood were unremarkable for any untoward events or chronic illness. The patient denied taking any medications known to precipitate her clinical condition. She was neither a hypertensive nor a diabetic.

Physical examination showed normal vital signs and she was a febrile. Systemic examination was unremarkable. Laboratory findings included Hb 8.3g/dl, total white cell count 13,100 cells/cu mm, with neutrophil count of 80%, urea nitrogen 40 mg/dl, creatinine 9.1 mg/dl, random plasma glucose 120 mg/dl, sodium 146 mEq/l, and potassium 7.7 mEq/l. Antistreptolysin O titres, troponin I levels, and calcium were within normal range. Blood gas showed pH 7.20, pO_2 109 mmHg, pcO_2 55 mmHg, bicarbonate 16.2 mEq/l. ECG showed LBBB with left axis deviation, secondary ST-T changes (Fig. 1). 2D echocardiogram was unremarkable. Chest X-ray showed that the heart size was slightly increased with no abnormalities in lung fields. USG abdomen showed bilateral small kidneys with grade 3 parenchymal changes.

She was initially treated with calcium gluconate, insulin with glucose, salbutamol nebulisation, and sodium polystyrene sulfonate. Continued treatment with drugs did not normalise the serum potassium and the patient then was kept on haemodialysis, with which her serum K^+ levels were reduced to normal, with normal ECG findings (Fig. 2).

In the clinical background of CKD and absence of known precipitating factors for increased K^+ levels, her hyperkalaemia is attributed to CKD. As the patient had no risk factors for cardiac conduction blocks, her ECG findings of LBBB in addition to other changes, are attributed to hyperkalaemia. Among hyperkalaemic ECG changes, LBBB with left axis deviation is rarely reported in the literature, but was found in our patient.

Discussion

Under normal circumstances renal excretion accounts for

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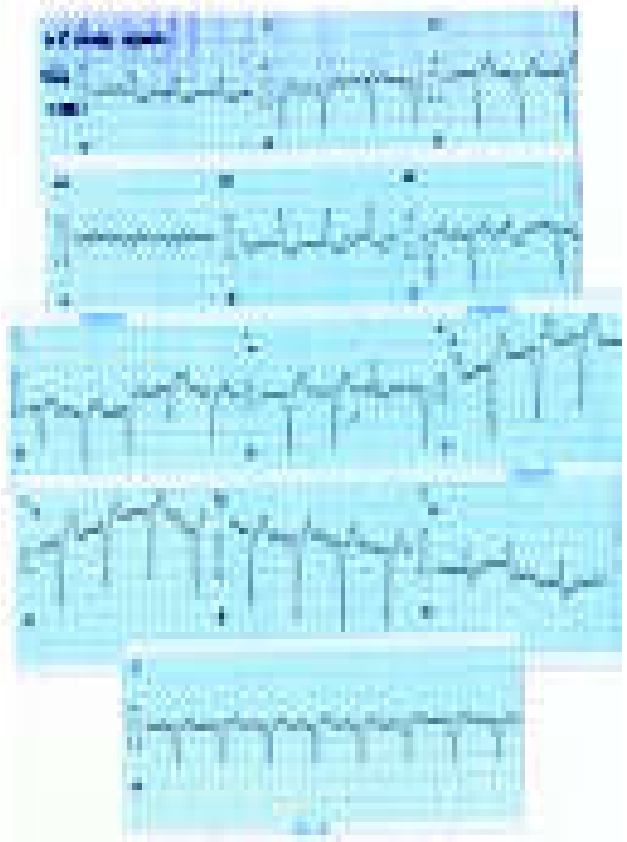


Fig. 1:

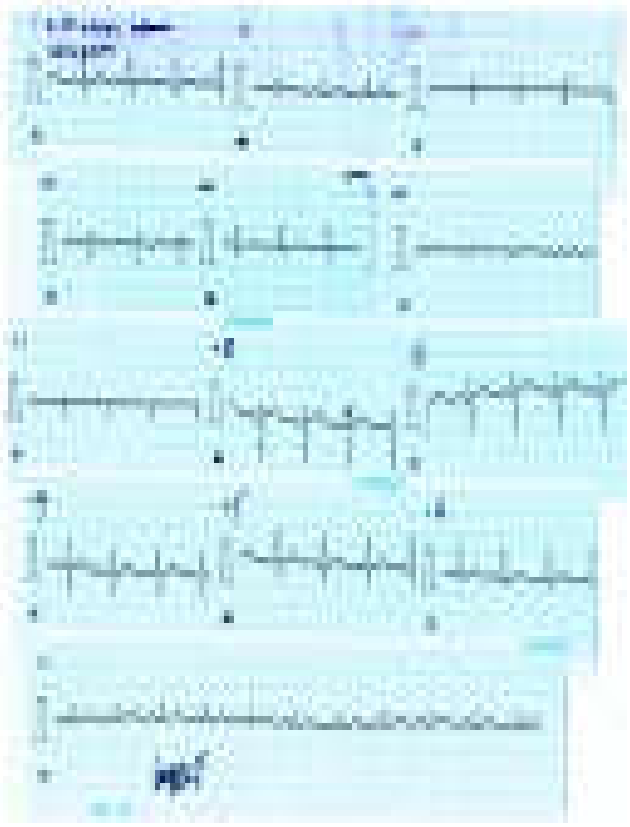


Fig. 2:

approximately 90% of daily potassium. As renal function declines, a greater fraction of the filtered load is excreted and serum K^+ levels do not rise until renal function declines to less than 25% of normal[2].

Cardiac toxicity

Electrophysiologic effects of hyperkalaemia include a reduction in resting membrane potential, a decrease in rate of rise of the action potential and a decrease in conduction velocity. A high concentration of extracellular potassium slows impulse conduction through all cardiac tissue, which accounts for a number of ECG findings. Bundle branch block is a manifestation of delay in activation of one of the ventricles that has been attributed to a direct electrophysiologic effect or subendocardial ischaemia from hyperkalaemia. The disproportionate conduction delay in the bundle branch system occurs more often in the right than in the left, unlike in our patient who had LBBB pattern[3]. Depression of conduction in the His – Purkinje system is a potential explanation for the right or leftward deviations in the frontal plane QRS axis, that sometimes occur in hyperkalaemic patients.

The hyperkalaemic ECG changes range from peaked T-waves, loss of P-waves, prolonged QRS complex, ST-elevations, escape beats and escape rhythm, sine wave, ventricular fibrillation, asystole, axis devations, bundle branch blocks, and fascicular blocks[4]. ECG alterations are also associated with sinus node depression, escape rhythms, and malignant ventricular arrhythmias (Table I). Usual order of appearance of ECG changes is tall T-waves, QRS widening, loss of P-wave, ST-elevation with "pseudo infarction" pattern, sine wave, and eventual asystole[5].

Correlation of ECG changes with serum K^+ levels

In a study of 27 patients with ECG changes of hyperkalaemia, elevated serum K^+ levels were found in 22 patients (82%). On the other hand, in 39 patients with hyperkalaemia, ECG showed agreement in only 21 (54%). In a retrospective study, ECG changes were seen in 43% of patients with serum K^+ ranging from 6.0 - 6.8 mEq/l, and in only 55% of patients with value of 6.8 mEq/l or greater. Another study documented that ECG changes were associated with serum K^+ 6.8 - 7.6 mEq/l, and found consistent above levels of 7.8 mEq/l. In one more study of 292 patients with hyperkalaemia, only 40 abnormal ECGs were found[5]. In this study, peaked T-waves, most frequent ECG change was seen in only two patients with mid levels (5.0 - 6.9 mEq/l) of

hyperkalaemia and prolonged PR interval was seen in all ranges of serum K^+ levels (Table II).

Table I: Electrocardiographic manifestations of hyperkalaemia[1].

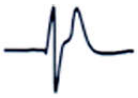
Serum potassium	ECG manifestations	Common ECG appearance
Mild (5.5 - 6.5 mEq/l)	Peaked T-waves Prolonged PR segment	
Moderate (6.5 - 8.0 mEq/l)	Loss of P-wave Prolonged QRS complex ST-segment elevation	
Severe (> 8.0 mEq/l)	Sine wave Ventricular fibrillation Asystole axis deviations Bundle branch blocks Fascicular blocks	

Table II: Serum potassium levels by ECG findings reported in a study[5].

Serum K^+ level	Peaked T-waves	Prolonged QRS	Prolonged QTc	Prolonged PR interval
5 - 5.9	1	5		10
6 - 6.9	1	2	1	10
7 - 7.9		1		4
8 - 8.9				1
Total	2	8	1	25

In general, a correlation can be observed between increasing abnormalities of ECG pattern and increasing serum K^+ concentrations; however, patient-to-patient variability is high. ECG changes might be subtle or even absent, further complicating the diagnosis. Thus ECG findings might not be sensitive in detecting mild and moderate hyperkalaemia, as documented in many studies.

Cause of poor correlation

It was documented in many studies that there was lack of confirmity of ECG manifestations with serum K^+ levels and this disparity was attributed to the presence of ECG alterations from other causes or to concomitant abnormalities of other electrolytes. In nephrectomised animals or in the presence of renal disease with acidosis, small increases in the serum K^+concentration may quickly alter the K_e/ K_i ratio and thus produce early and typical changes of hyperkalaemia. Contrariwise, in the presence of alkalosis with intact renal regulatory mechanism, a disturbance of the K_e/ K_i ratio may not occur until there is marked depletion of the body potassium and ECG changes can be expected to be delayed. Thus it is conceivable that the effects of the electrolyte derangement on the ECG may depend to a significant degree on the presence or absence of renal regulation of serum electrolytes[6].

Cardiac conduction blocks

Among hyperkalaemic changes, LBBB is a rare report in the literature and usually associated with severe hyperkalaemia (> 8.0 mEq/l). Bashour *et al* reported 12 patients with conduction blocks in hyperkalaemia with isolated left posterior hemiblock (LPHB) in 4; isolated left anterior hemiblock (LAHB) in 2; RBBB with LAHB in 2; RBBB with LPHB in 1; LBBB with abnormal left axis deviation in 2; and advanced A-V block in 1[7].

Ohmae *et al* reported 2 cases of hyperkalaemic ECG changes with RBBB with left axis deviation in one case and complete heart block in the second case, which disappeared with treatment of hyperkalaemia. Punja *et al* (1973), Katsikas and Goldsmith (1971), Weidner *et al* (1978), Lichstein *et al* (1976), and Shapiro (1979) each reported one case of RBBB with marked left axis deviation. A case of hyperkalaemic cardiac arrest in a 70-year-old man was reported, and the patient survived with resuscitation. Hyperkalaemia appears to potentiate subclinical conduction abnormalities especially in the His-Purkinje system.

Conclusion

ECG changes of hyperkalaemia are frequently consistent at higher levels of serum K^+ (≥7.8 mEq/l) and often progressive[8]. Eventhough most characteristic hyperkalaemic ECG changes are peaked T-waves and widening of QRS, appearance of ECG finding vary widely at a given concentration of serum K^+. Among hyperkalaemic ECG changes, conduction blocks are infrequent and also LBBB is rare compared to RBBB. LBBB, which is a rare report in literature, was documented in our patient, in addition to the other ECG findings.

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"Nations are many, but Earth is one;
Beings are many, but Breath is one;
Stars are many, but Sky is one;
Oceans are many, but Water is one;
Religions are many, but God is one;
Jewels are many, but Gold is one;
Appearances are many, but Reality is One."

– Sri Sathya Saibaba.

CASE REPORT

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An unusual case of misplacement of internal jugular double lumen dialysis catheter into ipsilateral subclavian vein in reverse direction

*Rohit Rungta**

Abstract

Misplacement of central venous catheter (CVC) inserted into the subclavian vein (SCV) and internal jugular vein (IJV) is a known and dreaded complication. The most common misplacement of the SCV catheter is into the IJV (5.4%) and does not vary with the side of insertion or whether the head is turned towards or away from the side of insertion[1]. The exact incidence of misplacement of IJV catheter into the SCV is not known and very few cases have been reported till date. Our case report is about misplacement of catheter in the reverse direction towards the axillary vein (reverse direction) inserted through IJV.

Keywords: Malpositioning, IJV, SCV, dialysis catheter.

Introduction

Percutaneous central venous catheterisation is now a common procedure for obtaining a temporary access for haemodialysis and also to buy time for the arterio-venous fistula to mature.

CVC is also used for perioperative care of major surgical patients, in intensive care monitoring, for long-term hyper-alimentation and also for securing a central vein for rapid restoration of blood volume in a case of unexpected acute blood loss.

Advantages of internal jugular vein cannulation relate to its consistent, predictable anatomic location, its valveless course to the superior vena cava and right atrium, the possibility of repeated cannulation, and low incidence of complications in an experienced hand. Placement of CVC is a technically challenging procedure. Reported incidence of malpositioning of CVC varies extremely widely from a range of < 1% to > 60%[2,3]. Most common misplacement is towards ipsilateral IJV for catheter inserted through SVC.

Misplacement of CVC inserted through IJV approach towards axillary vein instead of right atrium is very unusual. We report one such unusual case occurring in the ICU setting.

Case presentation

A 45-year-old male, a case of chronic kidney disease on inadequate haemodialysis came to the ER with dyspnoea and irrelevant talking since the last 2 days. The patient was haemodynamically stable with pulse 90 b/m, BP 126\70. His right internal jugular access was in place since the last 3 months and was removed only recently as he had complained of persistent fever since the last few days, and a right radio cephalic fistula was created.

On examining the patient, we came to the conclusion that the patient might be in uraemic encephalopathy since he had not had haemodialysis since the last 15 days. It was decided to give haemodialysis promptly to the patient. Since the RIJ catheter was in situ for last 3 months it was decided to cannulate the left side for temporary access.

CVC inserted through left-sided internal jugular vein approach went through single puncture. Guide wire went in freely. Adequate backflow of blood and free inflow of normal saline confirmed intravenous position of central

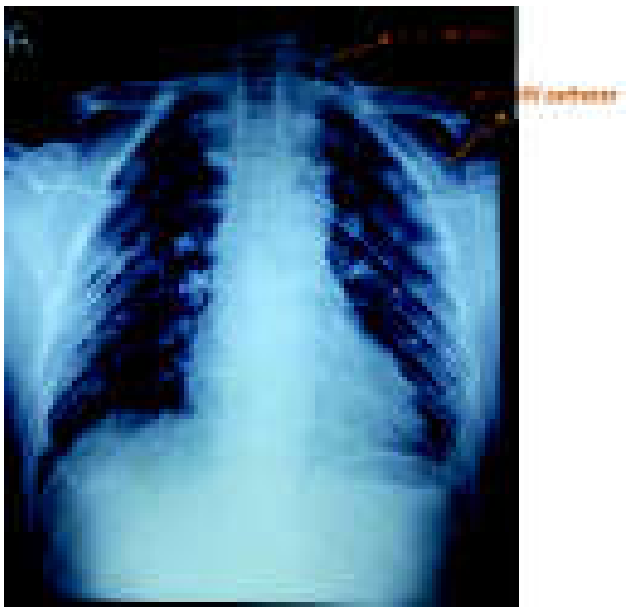

Fig. 1: *IJV catheter tip in retrograde position in the subclavian vein.*

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vein catheter. Chest X-ray was advised and so was haemodialysis.

Post-procedure chest X-ray was done which showed to our surprise that the catheter tip was placed in retrograde position in the subclavian vein as shown in Fig. 1.

The patient was transferred back to the operating room and the catheter was partially withdrawn over a guidewire using an image intensifier. At that time it became difficult to pass the guidewire beyond the junction of IJV and SCV. Every time an attempt was made, the guidewire was deflected into the SCV. After gentle manipulation, the guidewire entered medially into the brachiocephalic vein but the catheter could not be advanced over it. The guidewire along with the catheter was partially withdrawn and the catheter was respositioned keeping its tip proximal to the site of the suspected stenosis. The catheter was used for haemodialysis without any complication.

Discussion

Central venous catheter insertion is a common procedure used as a temporary access for haemodialysis, in monitoring CVP, administration of some drugs, blood and blood products, antineoplastic treatment, parenteral nutrition, and bone marrow transplantation. Central venous catheters can be centrally or peripherally inserted; however, the commonly referred technique is the internal jugular or subclavian veins. However, these procedures are not without complications, e.g., arterial puncture, malposition, pneumothorax, chylothorax, vein and nerve damage, infection, thrombosis, malposition, folding of the catheter, haemothorax, cardiac tamponade, air embolism, arrhythmia, and death[1].

Catheter misplacement is a known complication of central venous catheterisation[2] though uncommon and detected by immediate check chest X-ray or USG guided placement. The most common cause of early malfunctioning of the central venous catheter is related to its misplacement[3]. Central venous catheter tip placement at the junction of SVC and right atrium is important for good pump speed during haemodialysis[4]. A misplaced catheter tip not only defeats the purpose but also predisposes it to the risk of obstruction, clotting, thrombophlebitis, erosion of the venous wall[5,6]. Most common of all misplacements is the cephalad insertion into ipsilateral IJV via subclavian approach. Paw[7] stated that catheterisation via the left internal jugular vein results in more misplacement and vascular perforation than catheter placed from the right internal jugular vein. Other sites for misplacements include azygous vein, thymic vein, contralateral subclavian vein[8]. According to Muhm *et al*[9], the frequency of malpositioning was related to the anatomic approach and the catheter type used, but not to the physician's experience. Their reported respective incidences were 4.12% for the left internal jugular access, but were lower for the right internal jugular (1.1%); misplacement was more frequent with soft silicone catheters (2.53%) than with semi-rigid catheters (0.79%). Retrograde malpositioning of CVC in the axillary vein is a very unusual presentation as in our case report. Studies have hypothesised that the final position of the catheter tip depends on the course the guide wire takes which is influenced by the initial orientation of J type guide wire tip during the subclavian approach.

In a randomised controlled study, the authors suggest that keeping the guidewire J tip directed caudally increases the correct placement of the CVC towards the atrium[10]. Even use of USG guided insertion is controversial. Some suggest USG improves success rate of insertion performed by a less experienced operator. Others suggests that it has no significant effect on catheter insertion. The USG guided technique is a safer procedure especially in older patients; it affords an easier and more rapid cannulation of a central vein, drastically reducing major and minor complications[11].

Catheter placement is a blind procedure and misplacement of CVC remains a known but uncommon complication as in our case report showing unusual misplacement. Determination of the catheter position by chest X-ray should be considered not only when mechanical complications cannot be excluded, aspiration of venous blood is not possible, or the catheter is intended for central venous pressure monitoring, high flow use or infusion of local irritant drugs, but as a routine post-procedural investigation[12].

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"We never really encounter the world,
all we experience is our nervous system."

– THE BHAGAVAD GITA.

CASE REPORT

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Atelectasis with acute liver failure in a patient of scrub typhus

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Abstract

Atelectasis is a rare complication of scrub typhus. Only a few cases of scrub typhus complicated by atelectasis have been described in the literature. Here we report the case of a patient with scrub typhus complicated by atelectasis and acute liver failure (ALF). Due to non-specific clinical manifestations and lack of accessibility to facilities for diagnosis in developing countries, there is a high chance of misdiagnosis during the early stage leading to increased morbidity and mortality.

Keywords: Scrub typhus, atelectasis, acute liver failure.

Introduction

Scrub typhus is an acute febrile illness caused by *Orientia* (Rickettsia) *tsutsugamushi*. It is an important consideration in the differential diagnosis of acute febrile illness in eastern Asia and the western Pacific region, from Korea to Australia and from Japan to India and Pakistan. *O. tsutsugamushi* is transmitted to humans by the bite of a larval-stage trombiculid mite or chigger. The incubation period is 5 - 10 days. Clinical manifestations are fever, skin rash, eschar, and varying degree of respiratory distress[1].

The chest abnormalities of scrub typhus reported in the literature are interstitial pneumonia, cardiomegaly, pulmonary oedema, pleural effusion, hilar adenopathy, and focal atelectasis[2-3].

Atelectasis is a rare complication of scrub typhus and only a few cases of this disease complicated by atelectasis have been reported in the literature[4].

We report a case of scrub typhus with atelectasis and ALF in the same patient.

Case report

A 17-year-old male student was brought to our hospital on July 7, 2014 with complaints of high-grade fever, jaundice, and altered sensorium. The illness had started with a high-grade fever associated with sweating, headache, cough, and muscle pain about 7 days prior to presentation. The patient had consulted a local physician who prescribed an antibiotic and antipyretic, but he was not relieved. As the condition of the patient deteriorated, he was brought to our hospital in altered sensorium and hence was admitted.

The patient was tachypnoeic, restless, jaundiced, and had altered sensorium.

On general examination there was icterus, cervical and inguinal lymphadenopathy, blood pressure of 100/60 mmHg, pulse rate of 118/min, respiratory rate of 30/min, and temperature of 103.5° F. There was 1 cm sized black crusted ulcer (eschar) in the right mammary area and in left lower limb (Fig. 1).

On chest examination, there was shifting of trachea to the right side with flattening of chest, restricted movement and absent breath sounds on the right side.

The liver was palpable 2 cm below the right costal margin.

The Glasgow coma score (GCS) was 8: E2M4V2. His neurological examination revealed no neurological deficit. Bilateral plantars were mute. The pupils were bilaterally equal in size and normally reactive to light. No signs of

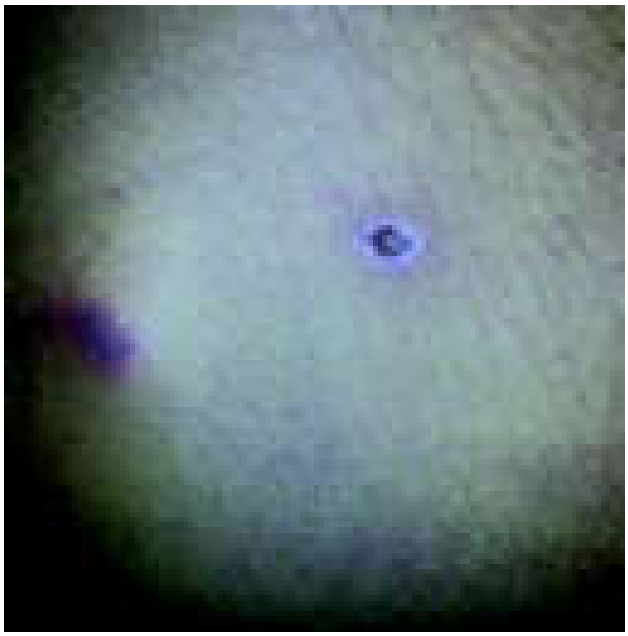

Fig. 1: *Eschar on right mammary area.*

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meningeal irritation were present. Fundus examination revealed no abnormality.

There was a history of going to jungle for jhum cultivation about one week prior to appearance of symptoms.

Routine laboratory evaluation showed a haemoglobin of 14 g%, white blood cell count of 13,000/cu mm (85%, neutrophils, 15% lymphocytes, 01% monocytes, and 02% eosinophils), a platelet count of 160,000, and random blood sugar of 91 mg%, with serum urea level of 103 mg/dl and serum creatinine level of 1 mg/dl. Antibody test for scrub typhus was positive. Peripheral blood smear for malarial parasites, serological test for leptospirosis, hepatitis B surface antigen test, hepatitis C virus test, HIV antibody test and the Widal test were all negative. Liver function test (LFT) showed total bilirubin of (18.4 mg%), aspartate aminotransferase (AST: 812 IU/l), alanine aminotransferase (ALT: 209 IU/l), and alkaline phosphatase (ALP: 1258 U/l); serum albumin was (3 g%). The cerebrospinal fluid (CSF) examination was normal.

Chest X-ray showed segmental collapse of the right upper lobe (Fig. 2). An ultrasound examination of the whole abdomen revealed hepatosplenomegaly. MRI of brain was normal.

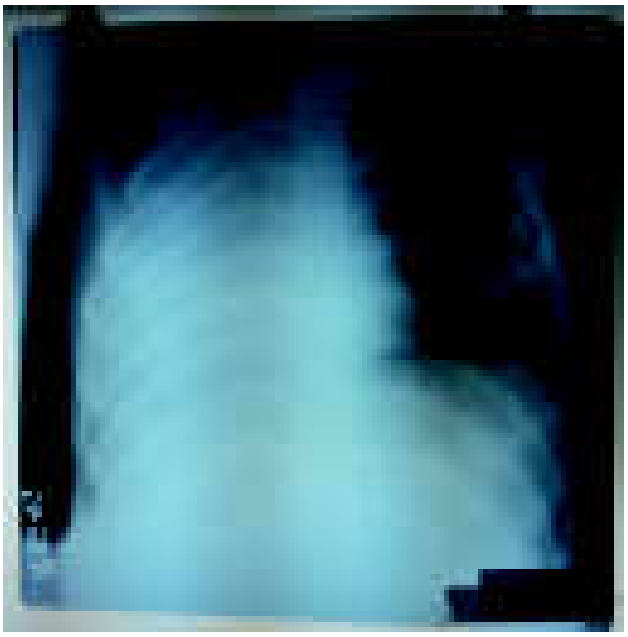

Fig. 2: *Chest X-ray showing collapse of right upper lobe.*

A diagnosis of scrub typhus with focal atelectasis of the right upper lobe and acute liver failure was made.

The patient was started on doxycycline 100 mg twice daily, along with other supportive measures. He responded and improved subsequently.

After one week his liver function test improved with total bilirubin of 5.6 mg%, AST level of 170 IU and ALT level of 113 IU. The repeat chest X-ray showed normal study (Fig. 3).

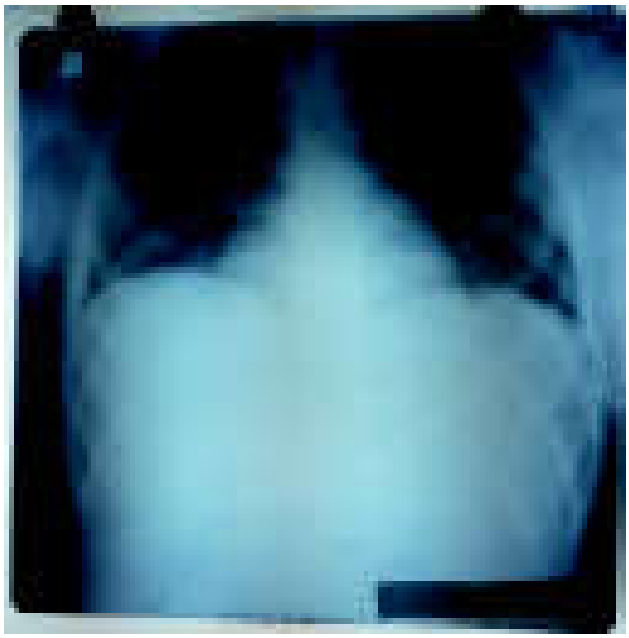

Fig. 3: *Repeat chest X-ray after one week was normal.*

The patient attended a check-up visit at the medicine out-patient department 2 weeks after discharge and had by now made a full recovery.

Discussion

Fever, sore throat, cough, myalgia, headache, rash, and eschar are the common clinical signs and symtoms of scrub typhus[5]. In our case, all these features were present except for rash. The presence of an eschar may be considered the most important clinical finding for the diagnosis of scrub typhus[6].

Acute liver failure (ALF), is often associated with scrub typhus. ALF is defined as encephalopathy or jaundice with a marked increase in liver enzyme levels and is often associated with scrub typhus[7].

The incidence of the chest radiographic abnormalities for patients with scrub typhus varies from 67.5 - 78%. The chest abnormalities of scrub typhus reported in the literature are interstitial pneumonia, cardiomegaly, pulmonary oedema, pleural effusion, hilar adenopathy, and focal atelectasis[2-3].

Song *et al* reported 12/101 (11.8%) cases of focal or subsegmental atelectasis. The patients with atelectasis had higher incidence of hypoxia, hypotension, severe thrombocytopenia and hypoalbuminaemia which predisposed to development of interstitial pneumonia (IP).

The patients with IP tended to have a greater incidence of acute renal failure than for those patients without IP. Furthermore, the hospitalisation duration of the patients with IP was longer than that of the patients without IP, and mortality tended to be higher in the patients with IP than for the patients without IP. They also compared other radiographic findings between the patients with or without IP. The patients with IP also had higher incidences of pleural effusion, cardiomegaly, pulmonary alveolar oedema and hilar lymphadenopathy than for the patients without IP[4].

Severe cases in scrub typhus typically include encephalitis and interstitial pneumonia due to vascular injury[8].

Therefore, IP is associated with severity of the disease of scrub typhus.

In conclusion, atelectasis is a rare manifestation of scrub typhus, which predisposes to the development of interstitial pneumonia. Its early diagnosis and prompt treatment prevents the increased morbidity and mortality associated with interstitial pneumonia for patients with scrub typhus.

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"Now I see the secret of making the best person:
It is to grow in the open air and to eat and sleep with the earth."

– Walt Whitman.

CASE REPORT

JIACM 2016; 17(2): 145-47

Pituitary apoplexy in vivax malaria with thrombocytopenia

*Rajesh Deshwal**

Abstract

Vivax malaria causing complications akin to falciparum has been reported earlier but pituitary apoplexy has not been reported neither with vivax nor with falciparum. Hyponatraemia as a consequence of pituitary apoplexy and high index of suspicion in picking-up these cases is stressed.

Keywords: Hyponatraemia, multiorgan dysfunction, complicated malaria.

Introduction

Vivax malaria causing complications akin to falciparum is well documented by now but malaria causing pituitary apoplexy has not been documented in the literature so far. This case is being presented to sensitise the clinicians in picking-up the diagnosis with unresponsive hyponatraemia in the background.

Case report

A 65-year-old female patient admitted with history of high grade, intermittent fever with chills of 10 days duration. Denied any history of respiratory, abdominal and urinary complaints. Yellowish discoloration of sclera was noticed by her family members few days prior. Divulged history of loss of appetite, weakness, fatigue, and somnolence. Past history was unremarkable except for some prescriptions for acute gastritis. Had achieved menopause 12 years back. Clinical examination revealed temperature 101° F, pulse 128/min, respiraory rate 26/min, BP 100/70 mmHg, SpO_2 98% at room air. Tongue was dry and skin turgor was reduced. Icterus was noticed. There was no pallor, pedal oedema, cyanosis and jugular venous pressure was normal. Systemic examination was documented as normal. Investigations revealed Hb - 11.1 gm%,TLC - 2,100/cu mm, polymorphs - 80%, platelets - 60,000/cu mm, blood urea - 65 mg% and serum creatinine - 1.6 mg%, serum bilirubin - 6.2 mg% direct - 2.4 mg%, AST/ALT - 117/126 U/L, alkaline phosphatase - 147 U/L. Blood smear showed asexual forms of vivax and rapid antigen test (SD BIOLINE Malaria Antigen P.f./P.v. test kit) was positive for vivax and negative for falciparum. Widal and blood cultures were negative, HbsAg was positive, HCV and HIV were negative. Dengue serology (IgM, IgG) was negative too. Serum sodium, potassium and calcium were 129 mg%, 4.3 mg%, and 8.9 gm% respectively. Chest radiograph was reported as normal.

She was started on injectable artesunate-based combination therapy along with sulfadoxine-pyrimethamine and doxycycline in usual dosages with added oral salt and other supportive therapy as indicated. By next day patient was well hydrated, afebrile, maintaining blood pressure, started eating, and subjectively felt better. Her serum sodium levels recovered to 134 mg%. Over the next 24 to 48 hours, patient remained afebrile, conscious and oriented, eating normally, and her liver and kidney parameters returned towards the better side (blood urea/creatinine 52/1.2 mg%, serum bilirubin 2.4 mg%, AST/ALT 64/68 U/L) but platelet count had dipped to 40,000/cu mm.

On day 4 of admission though she remained afebrile, her sensorium started deteriorating and she became restless, trying to run-off the bed. She has had a few episodes of vomiting too. Her serum sodium levels were again noticed to be low (116 mg%), which were corrected again with 3% hypertonic saline and oral salt to normal levels over the next 2 days but patient remained restless. Hyponatraemia as a cause of restless state seemed unlikely, so a contrast-enhanced computed tomography scan of brain was ordered which revealed a well defined 13.6 x 13.6 x 14.9 mm, non-enhancing hyperdense lesion in sellar and suprasellar region suggestive of haemorrhagic pituitary macroadenoma (Fig. 1). Hormonal analysis revealed FSH 9.12 mIU/ml (23.00 - 116.30), LH 2.74 mIU/ml (15.90 - 54.00), serum cortical 147.17 µg/dl (4.30 - 22.40), serum T3 0.34 ng/ml (0.60 - 1.81), T4 5.00 µg/dl (5.01 - 12.45), and TSH 0.25 uIU/ml (0.35 - 5.50).

Discussion and review of literature

Pituitary apoplexy is a rare but life-threatening medical emergency that results from either a sudden haemorrhage or infarction in a pituitary tumour. The incidence of pituitary apoplexy varies from 1.9% to 6.8%[1,2]. Among pituitary tumours, nonfunctioning pituitary macroadenomas are the most commonly involved in apoplexy. The majority of

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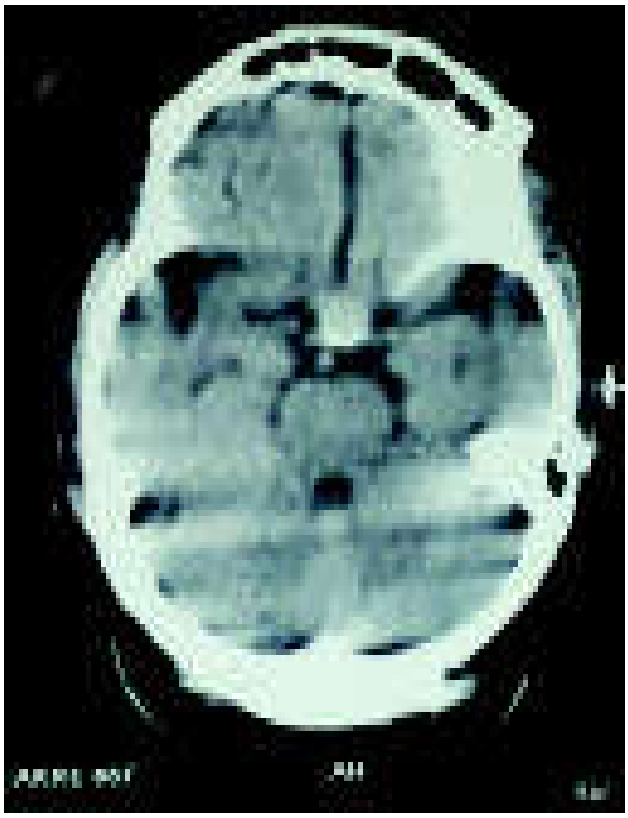

Fig. 1: *CECT of brain showing well defined, non enhancing hyperdense lesion in sellar and suprasellor region suggestive of haemorrhagic pituitary macroadenoma.*

patients who present with pituitary apoplexy did not receive a diagnosis of pituitary adenoma prior to their presentation suggesting that pituitary apoplexy may be the initial manifestation of undiagnosed pituitary tumours[3]. The most common presenting symptom of pituitary apoplexy is headache which probably results from stretching and irritation of the dura mater in the walls of the sella supplied by the trigeminal nerve meningeal branches. Nausea and vomiting are also frequent symptoms.

The most fearful complications of pituitary apoplexy are the ophthalmic and hormonal ones. Compression of the optic chiasm and optic nerve may lead to decreased visual acuity, bi-temporal hemianopia and sometimes complete blindness. Compression of the adjacent cavernous sinus and its nerve content (located on both sides of the sella) may result in ophthalmoplegia, particularly the third cranial nerve because of its outer location[4]. Deficiency of the anterior pituitary hormones is a frequent finding and may lead to catastrophic outcome. ACTH deficiency is the most commonly encountered and the most serious hormonal abnormality in pituitary apoplexy which may result in adrenal crisis and hypotension. In our patient, blood samples for hormonal analysis were drawn after patient was started on IV hydrocortisone, hence serum cortisol values were higher. Other hormones like TSH, LH, FSH, GH could also be affected as were documented to be low in our patient also. Pituitary MRI is the diagnostic tool of choice for pituitary apoplexy[5]. Hyponatraemia may result from adrenocorical insufficiency or inappropriate ADH secretion from the posterior pituitary gland. Repeated episodes of hyponatraemia in our patient were probably because of adrenocortical insufficiency. *Plasmodium vivax* or *falciparum* as a cause of pituitary apoplexy has not been reported in literature earlier and this is the first case being reported. Mishra *et al* have reported a dengue haemorraghic fever causing pituitary apoplexy where the platelet count was 47,000/cu mm[7]. Vimal Kumar *et al* also reported a dengue haemorraghic fever with platelet count of 45,000/cu mm causing pituitary haemorrhage with reversible vision loss[8]. Shwu-Jiuan Chen *et al* reported a case of hyponatraemia in pituitary apoplexy in an elderly individual who had presented with a 2-week history of weakness, dizziness, nausea, poor appetite, and general fatigue progressing to somnolence[9]. *P. vivax* malaria is causing complications akin to falciparum, and benign nature of the illness is now a thing of the past[10]. Multi-organ dysfunction in vivax malaria has been documented in earlier studies[11] as was evidenced in our case too, where we had liver, kidney dysfunction along with severe thrombocytopenia.

Conclusion

Severe vivax malaria leading to multiorgan dysfunction, hyponatraemia, and thrombocytopenia which eventually lead to haemorrhage in a pituitary macroadenoma is reported. This is the first ever reported case in medical literature where thrombocytopenia due to vivax malaria has led to pituitary apoplexy.

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"Cultivate tolerance, sincerity, compassion, contentment, and truthfulness...
You do not consist of – earth, water, fire, air, or even ether.
To be liberated, know yourself as consisting of consciousness,
the witness of these."

– Ashtavkra Gita, 1.2-3.

SHORT COMMUNICATION

JIACM 2016; 17(2): 148-51

An attempt to develop the management guidelines of vitamin D supplementation in patients with primary hyperparathyroidism and co-existent vitamin D deficiency in a district general hospital in the United Kingdom

I Talapatra, IPM O'Connell***

Introduction

Primary hyperparathyroidism (PHPT) and vitamin D deficiency often co-exist. Serum calcium level is high in PHPT. Vitamin D regulates the calcium balance in the body. The active hormonal form, 1,25-dihydroxyvitamin D3, causes calcium absorption in the intestine, calcium reabsorption in the distal kidney tubules, and bone calcium mobilisation. Hence many doctors are reluctant to supplement vitamin D in PHPT because of the possibility of further worsening of the already existing hypercalcaemia. However, studies have shown that vitamin D supplementation is necessary if its level is low in PHPT, although no clear guidelines exist in this respect. Therefore, we tried to find out what we have done so far to most of our patients with these two co-existing conditions with a view to developing a protocol in the near future and performing an audit later on against set guidelines to improve further our practice with regard to management of such patients.

Aims

1. To find out if vitamin D was estimated in patients diagnosed earlier with primary hyperparathyroidism (PHPT) and were seen on follow-up between January and May 2015.
2. To find out if these patients with PHPT and low vitamin D were treated with vitamin D supplementation (cholecalciferol).

Methods

Case notes of patients with primary hyperparathyroidism and with eGFR > 30 ml/min who attended the clinic between 1st January 2015 and 31st May 2015 were looked into for the purpose of the audit.

Guidelines

No national guidelines in the UK are present with regard to measurement and supplementation of vitamin D in patients with primary hyperparathyroidism. Therefore, a proper audit could not be carried out. However, local guidelines of a few hospitals in the UK are in place.

Key words: Hyperparathyroidism, vitamin D, calcium, parathyroidectomy, cinacalcet.

Discussion

Vitamin D deficiency commonly co-exists with primary hyperparathyroidism and it is essential to replenish it. Vitamin D is metabolised in the liver to form 25-hydroxy vitamin D followed by further hydroxylation in the kidneys by 1-alpha hydroxylase, under the control of parathyroid hormone, to produce 1,25-dihydroxy vitamin D. 1,25-dihydroxy vitamin D stimulates renal calcium absorption, bone calcium mobilisation, and calcium absorption in the intestine[1].

However, rather than 1,25-dihydroxy vitamin D which is the most potent vitamin D metabolite, level of the 25-hydroxyvitamin D is a better measure of the body's vitamin D stores[1]. The reasons for measuring 25-OH vitamin D rather than 1,25-dihydroxy vitamin D are as follows:

I. 1α hydroxylation of 25-hydroxy vitamin D can also happen in placenta, bone, skin, and granulomatous tissue (sarcoid, tuberculosis).

II. The rate of 1,25-dihydroxy vitamin D production by the kidneys can be influenced by the prevailing calcium and parathyroid hormone (PTH) concentration.

III. Short half-life of 1,25-dihydroxy vitamin D which is approximately 15 hours[2].

IV. Also, 25-hydroxy vitamin D needs to decrease to around 10 nmol/l for 1,25-dihyroxy vitamin D to decrease significantly.

Vitamin D deficiency and PHPT commonly co-exist for various reasons. Chronic vitamin D deficiency causes autonomous parathyroid gland stimulation with hyperplasia and adenoma formation[3-5]. The increased level of 1,25-

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dihydroxyvitamin D in PHPT also influences the overall vitamin D status. There is reduced formation of vitamin D in skin and inhibition of the production of 25-hydroxyvitamin D in the liver with increased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidneys[3-5]. Also, patients with PHPT have enhanced catabolism and inactivation of 25-hyroxy vitamin D. There is accelerated clearance and biliary excretion of the degradation products of 25-hydroxy vitamin D. Co-existing vitamin D deficiency may cause the serum calcium level to remain in the normal range, leading to problems with diagnosis. With regard to management, vitamin D repletion in patients with mild primary hyperparathyroidism may be done without worsening of the underlying hypercalcaemia. Literature review suggests that vitamin D-deficient patients with PHPT have larger parathyroid adenomas, higher levels of parathyroid hormone (PTH) and more frequent fractures than patients with normal vitamin D. Vitamin D supplementation causes reduction in PTH levels and bone turnover leading to increased bone mineral density (BMD) and reduced fracture risk[6,7,8]. Vitamin D-deficient patients undergoing parathyroidectomy are also at increased risk of post-operative hypocalcaemia and "hungry bone syndrome", and hence assessment of vitamin D is needed in all patients with primary hyperparathyroidism followed by supplementation, if necessary[5]. Vitamin D replacement can be done reasonably safely in PHPT till the corrected calcium reaches 3 mmol/l[9]. Generally in our hospital, in vitamin D deficiency (all causes), we use Pro-D3 (cholecalciferol): 40,000 units daily for 10 days and then a maintenance dose of 20,000 units every week usually for 6 months. According to the National Osteoporosis Society in the UK, 300,000 units of vitamin D is to be given in 6 weeks and then 800 - 4,000 units daily as maintenance[10]. However, no clear guidelines are available in the UK for supplementation of vitamin D in PHPT.

Criteria

1. To check if vitamin D level was assessed in patients with PHPT.
2. To check how long after diagnosis of PHPT was vitamin D estimated and whether replenishment was commenced.
3. What therapeutic dose of vitamin D was administered?
4. Whether vitamin D replacement was discontinued when serum calcium reached 3 mmol/l.

Results

1. Number of patients with PHPT studied: 22
2. Age: 30 - 50 yrs = 2, 50 - 60 yrs = 1, 60 - 70 yrs = 6, 70 - 80 yrs = 4, 80 - 90 yrs = 7, > 90 yrs = 2
3. Sex M: F = 2: 20
4. Number of patients in whom vitamin D level was checked: 19 out of 22 (see diagram 1)
5. How long after diagnosis of PHPT was vitamin D level checked?

   < 3 months = 9, 3 - 6 months = 2, 6 - 12 months = 2, > 1 yr = 6 (1 after 3 years, 1 after 6 years and 1 after 7 years)
6. Number of patients with low vitamin D (see diagram 2): 15 out of 19. All were treated with vitamin D supplements.
7. What dose of vitamin D was administered initially?

   3 patients = 400 IU daily, 9 patients - 800 IU daily, 3 patients = 20,000 IU weekly (see diagram 3); 1 mcg of colecalciferol = 40 IU
8. In how many patients did serum calcium go beyond 3 mmol/l and whether replacement therapy was stopped then?

In 3 out of 15 patients serum calcium reached > 3 mmol/l and vitamin D replacement was stopped (see diagram 4). 1 patient was on colecalciferol 400 IU daily and 2 patients were on 800 IU daily. These patients were referred for parathyroidectomy and treated with cinacalcet (a calcimimetic drug which lowers serum PTH and calcium) while awaiting surgery. However, of the 4 patients with no vitamin D deficiency, 2 had to be referred for surgery.

Follow-up measurement of vitamin D level was variable, usually after 1 and 6 months following commencement of treatment with vitamin D supplementation.

Diagram 1: *Showing the proportion of patients with PHPT in whom vitamin D was estimated.*

Summary

1. Vitamin D was checked in 19 out of 22 patients.

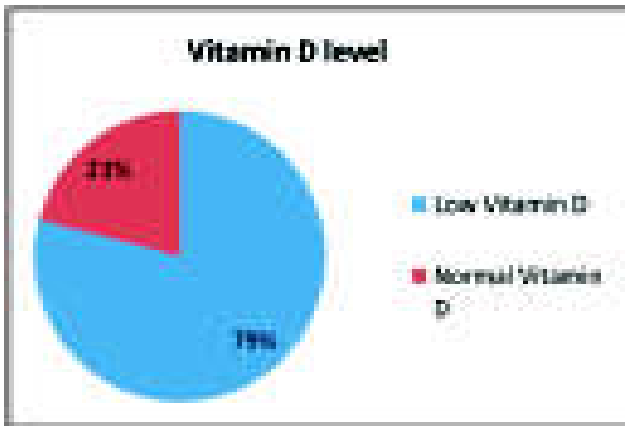

Diagram 2: *Showing the proportion of patients with PHPT in whom vitamin D was low.*

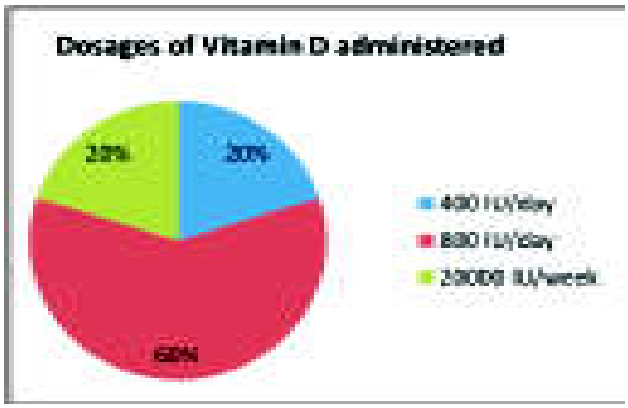

Diagram 3: *Showing different dosages of colecalciferol given to patients with PHPT and low vitamin D.*

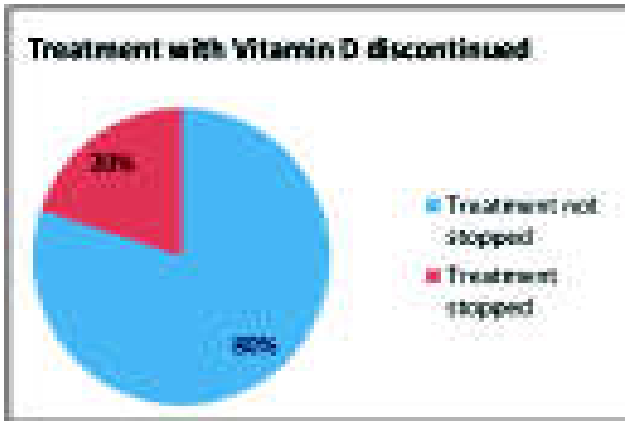

Diagram 4: *Showing the proportion of patients in whom vitamin D treatment was withdrawn.*

2. 11 patients had vitamin D checked within the first 6 months and altogether 13 patients had vitamin D checked within 1 year following the diagnosis of PHPT.
3. 15 out of 19 patients had low vitamin D.
4. All 15 patients were given vitamin D replacement but in varying dosages. Most patients (9 out of 15) had 800 IU daily.
5. In 3 out of 15 patients, serum calcium exceeded 3.0 mmol/l and vitamin D supplementation was stopped. These patients had to be referred for surgery.

Recommendations

Doctors are sometimes unwilling to administer vitamin D in patients with PHPT and co-existent low vitamin D because of the risk of exacerbation of hypercalcaemia. We recommend:

1. Vitamin D measurement is to be done in all patients with PHPT once the condition is diagnosed.
2. Supplementation of vitamin D is needed if it is found to be low.
3. A consensus with regard to proper guidelines is to be reached to manage patients with PHPT and low vitamin D in respect of the: (i) dose of vitamin D to be administered; (ii) duration of vitamin D administration; and (iii) frequency of blood tests for vitamin D monitoring.
4. Vitamin D supplementation is to be discontinued or vitamin D supplementation is to be continued with cinacalcet, once serum calcium reaches 3 mmol/l. This depends on the level of level of vitamin D achieved. Once the serum calcium is > 2.85 mmol/l (0.25 mmol/l or 1 mg/dl above the upper limit of normal), the patient needs to be referred for surgery.
5. Audit and re-audit in future against set guidelines of management (if the two conditions of PHPT and vitamin D co-exist) once they are established.
6. To continue to follow the guidelines mentioned in the NIH criteria of 1990, revised in 2002 and 2008 for referral for parathyroidectomy in asymptomatic PHPT[11].

In PHPT the patient is advised to remain active and drink plenty of water and stop lithium or bendroflumethiazide, if on any of these. The patient is commenced on an oral bisphosphonate if found to be osteoporotic on DEXA scan. If the serum calcium exceeds 3 mmol/l (12 mg/dl), the patient may require treatment with intravenous fluids and intravenous pamidronate. The medication cinacalcet works quite quickly in lowering serum calcium level.

Referral for parathyroidectomy is done if the patient is symptomatic from hypercalcaemia or in asymptomatic cases (following neck imaging with ultrasound or sestamibi scan for parathyroid, i.e., sestamibi parathyroid scintigraphy) if one of the underlying criteria is met as per the NIH

guidelines[11]:

i) Serum albumin-adjusted calcium > 0.25 mmol/l (1 mg/dl) above the upper limit of normal laboratory range.

ii) 24-hour total urinary calcium excretion is > 10 mmol (400 mg). Normal range is 2.5 - 7.5 mmol over 24 hours.

iii) Creatinine clearance decreased > 30%.

iv) eGFR < 60 ml/min.

v) Kidney stones.

vi) Low bone mineral density (T score < -2.5 at any site on DEXA scan).

vii) Age less than 50 years.

Also, the referral depends on the request of patient. The recently concluded 4th International Workshop has recommended in asymptomatic PHPT, inclusion of extensive evaluation of renal and skeletal systems in the guidelines for surgery[12].

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"You commit innumerable sins because of your desires and longing for Maya.
Your body will become a pile of dust;
death will eventually conquer you.
Abandoning your wealth and youth, you will have to leave with nothing."

– Guru Granth Sahib.

JIACM 2016; 17(2): 152

Arcus juvenilis – A sign not to be missed

PS Sreejith, M Mahesh**, CR Venkatesh****

A 38-year-old female patient was admitted with a clinical diagnosis of acute viral febrile illness. She recovered with appropriate supportive care. However, on routine examination she was noted to have a greyish white ring around the periphery of the cornea of her both eyes (Fig. 1). This was suggestive of arcus juvenilis. Ophthalmology consultation confirmed the diagnosis.

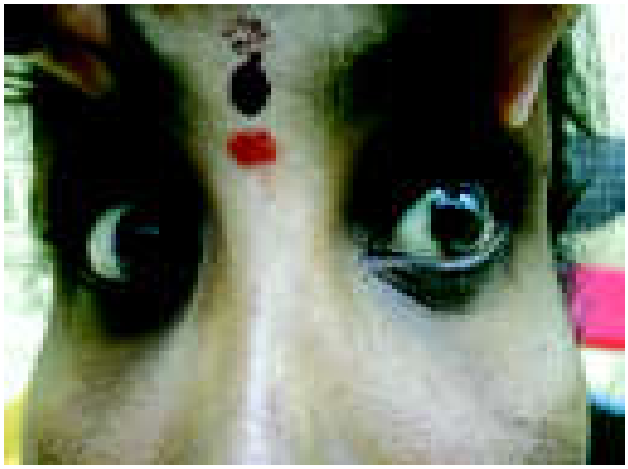

Fig. 1: *Eyes showing showing corneal arcus.*

In view of above finding, fasting lipid profile was done which revealed hypercholesterolaemia with total cholesterol of 267 mg/dl, LDL 155 mg/dl; and hypertriglyceridaemia with triglycerides at 349 mg/dl (Fig. 2). This fits into Frederickson type II b hyperlipoproteinaemia. Cardiac evaluation such as ECG, echocardiogram and Treadmill testing were normal. Further inquiry revealed history of sudden death of her elder brother at age 34 years. She was started on atorvastatin 10 mg/day and fenofibric acid 160 mg/day. She was advised diet regulation and was discharged with advise to be on regular follow-up.

Fig. 2: *Results of lipid profile.*

Corneal arcus (*anterior embryotoxon*) is a whitish ring of peripheral cornea separated from limbus by a clear zone. Both juvenile and adult forms represent paralimbal stromal accumulation of cholesterol ester, triglycerides and phospholipids[1]. Persons less than 40 years with corneal arcus have a significantly increased risk of coronary artery disease and they should be evaluated for hyperlipoproteinaemia[2].

Keywords: *Arcus juvenilis, hyperlipoproteinaemia, limbus sign.*

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"A man can be himself only so long as he is alone,
and if he does not love solitude, he will not love freedom,
for it is only when he is alone that he is really free."

– Arthur Schopenhauer.

MAGNEX

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  - Results
  - Discussion
  - Acknowledgment
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- This should be given on a separate page.
- Should not exceed 250 words for original article and 100 words for a case report, and should contain 3-10 keywords at conclusion of abstract.
- Should include background, aims of study, methodology, results, and conclusion. The problem(s) being addressed in the study, and conclusion of its result, must be expressed clearly in the abstract.

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- Discussion should avoid repetition of results or review of literature.
- Text should not contain data given in tables.
- Abbreviations must be avoided in title, subtitle, and summary.
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D. Statistical methods

- Describe methods used, in detail.
- Present the results in a logical sequence in the text, tables, and illustrations.
- In discussion, emphasise newer aspects of the study and the conclusions that follow from them.

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- Type each table double-space on a separate page.
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- Number the tables in Arabic numerals.
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- Do not use internal horizontal and vertical rules.
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- As far as possible, the figures should be professionally designed, on glossy paper, and large enough to be legible even after reduction, so as to fit the width of a single column.
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1. The Vancouver system of references should be used.
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3. The number of references should not exceed 30 for an original article, 10 for a short article, 8 for a case report, and 3 for a letter to the editor.
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The form of references is as follows:

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Indian Association of Clinical Medicine

Headquarters: P.G. Department of Medicine, S.N. Medical College, Mahatma Gandhi Road, Agra - 282 002, U.P.

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We hereby propose the admission of

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Name (in full): .....
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(Branch of Medicine for P.G. Degree)
University: .....
Year of obtaining the first Postgraduate Qualification: .....
Address: .....
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To the best of our knowledge and belief, the above particulars are correct and we consider him/her a fit and proper person to be admitted as Associate Life Member/Member/Fellow of the 'Association'.

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24th Annual Conference of the Indian Association of Clinical Medicine,
4th - 6th November, 2016 ● Gwalior, (M.P.)

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Registration Fee includes :

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